### 16.1.1 Protocol and Protocol Amendments

The latest version of the study protocol and all previous versions are provided on the following pages:

- V10.0, 10 Dec 2018 (Amendment 08)
- V9.0, 01 Feb 2017 (Amendment 07)
- V8.0, 02 Nov 2016 (Amendment 06)
- V7.0, 26 Sep 2016 (Amendment 05)
- V6.0, 29 Jun 2016 (Amendment 04)
- V5.0, 06 Feb 2016 (Amendment 03)
- V4.0, 05 Nov 2015 (Amendment 02)
- V3.0, 28 May 2015 (Amendment 01)
- V2.0, 21 Oct 2014 (revised original protocol)
- V1.0, 15 Jul 2014 (original protocol)

# REVISION HISTORY

**Revisions to Version 9.0**

**New version/date: Version 10.0/10 Dec 2018 (per Amendment 08)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Added an additional 24 months to the Extension Phase. | To continue to assess the long-term safety and tolerability of elenbecestat 50 mg per day in subjects who elect to continue with open-label treatment. | Synopsis<br>• Study Period and Phase of Development<br>• Objectives<br>• Study Design<br>• Duration of Treatment<br>• Endpoints<br>• Analyses<br>Section 9.1<br>Section 9.2.5<br>Appendix 6 |
| Revised interim safety assessments for Years 3 to 4 of the Extension Phase to be 4 months apart. | To reduce subject burden. | Synopsis<br>• Study Design<br>Section 9.1.3<br>Appendix 6 |
| Added that if subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator | To clarify that subjects would not need to withdraw from study. | Synopsis<br>• Study Design<br>Section 9.1.3<br>Section 9.5.1.5.7<br>Appendix 6 (Extension Phase Assessments) |
| Revised Visits 33 and 34 as visits in the treatment period. The Follow-up Visits at 4 weeks and 12 weeks will be renamed as Follow-up Week 4 Visit and Follow-up Week 12 Visit, respectively. | For clarity purposes. | Synopsis<br>• Safety Assessments (Extension Phase)<br>Section 9.5.1.5.1<br>Section 9.5.4.1<br>Appendix 6<br>• Table 14 |
| Revised Peripheral blood mononuclear cells (PBMCs) during the Extension Phase to be collected at baseline (Visit 21), 6 months (Visit 26), 12 months (Visit 28), and 24 months (Visit 32) only. | Based on new guidance from the DSMB. | Synopsis<br>• Safety Assessments (Extension Phase)<br>Section 9.2.5<br>Section 9.5.1.5<br>Appendix 6 (Extension Phase Assessments) |

**Revisions to Version 9.0**

**New version/date: Version 10.0/10 Dec 2018 (per Amendment 08)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | | • Table 13<br>• Table 14 |
| During the Extension Phase, lymphocyte subsets will be assessed during the first 12 months only. | Based on new guidance from the DSMB. | Synopsis<br>• Safety Assessments (Extension Phase)<br>Section 9.4.7<br>Appendix 2<br>• Listing 2<br>Appendix 6<br>• Table 13<br>• Table 14 |
| Removed requirement for treatment discontinuation based on amyloid-related imaging abnormalities or findings of average QTcF >500 msec. | To align with the safety criteria for discontinuation in the Phase 3 program | Appendix 6 (Safety-related criteria for discontinuation of study drug) |
| Added that any amyloid-related imaging abnormalities and treatment-emergent depigmentation/ hypopigmentation/vitiligo/loss of hair color will require collection of information sufficient to provide detailed description of the events treatment and outcome to the Medical Monitor for the study. | To ensure sufficient information is collected for full description of these events | Section 9.5.1.5 |
| Removed requirement for food while taking study drug. | To reduce patient burden as current clinical pharmacology data indicate that food has minimal pharmacodynamic impact. | Synopsis<br>• Study Treatments (Extension Phase)<br>Appendix 6 (Treatments) |
| Subjects with abnormal urine pregnancy test will have a serum pregnancy performed. | Correction in instruction | Appendix 6<br>• Table 14 |
| Added clarification that the clinical assessment of suicidal thinking and behavior will be conducted only at visits that do not include administration of the Columbia Suicide Severity Rating Scale (C-SSRS) and that a positive suicidality assessment | To clarify when the C-SSRS will be administered. | Synopsis<br>• Safety Assessments (Extension Phase)<br>• Safety Analyses (Extension Phase)<br>Section 9.2.5<br>Section 9.5.1.5 |

**Revisions to Version 9.0**

**New version/date: Version 10.0/10 Dec 2018 (per Amendment 08)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| from the subject or the caregiver/informant on the clinical assessment of suicidality (ie, a "yes" response on the clinical assessment of suicidal thinking and behavior) would trigger the C-SSRS to be administered. | | Section 9.5.1.5.11<br>Appendix 6 (Extension Phase Assessments)<br>• Table 14 |
| Added instruction that the investigator should review and determine whether positive assessments in suicidal thinking and behavior constitute an adverse event. | To ensure that any positive assessments in suicidal thinking will be assessed as potential adverse events. | Section 9.5.1.5.1 |
| Revised definition of Extension Phase Safety Analysis Set | Clarification | Synopsis<br>• Analysis Sets<br>Appendix 6 (Extension Phase Analysis Sets) |
| An editorial revision was made to remove "(E2609)" in the text of the protocol | Elenbecestat is now a recommended International Nonproprietary Name (rINN) | Throughout |
| Editorial changes | Correction | Throughout |

**Revisions to Version 8.0**

**New version/date: Version 9.0/01 Feb 2017 (per Amendment 07)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| An editorial revision was made to add "elenbecestat", the proposed International Nonproprietary Name (pINN) for "E2609"; grammatical, typographical, and formatting changes were also made. | The revision was made to provide consistency for current and future elenbecestat (E2609) clinical development documents. | All sections of the protocol that previously included "E2609" or required editorial revision |
| A Open-label Extension (OLE) Phase of up to 24 months was added to the protocol specifying that eligible subjects who elect to continue open-label treatment after completing Visit 20 will receive elenbecestat (E2609) 50 mg per day. A detailed description of the OLE Phase was added in Appendix 6.<br><br>An editorial revision was made referring to the original "study" (Prerandomization and Randomization Phases) as the "Core Study". | The OLE was added to assess long-term safety and tolerability of elenbecestat (E2609) 50 mg per day in subjects who elect to continue open-label treatment after Visit 20.<br>The editorial revision was made for clarity of presentation where description of the OLE procedures has been added. | Synopsis<br>• Study Period and Phase of Development<br>• Objectives<br>• Study Design<br>• Inclusion Criteria<br>• Exclusion Criteria<br>• Study Treatment<br>• Duration of Treatment<br>• Concomitant Drug/Therapy<br>• Assessments<br>• Endpoints<br>• Analysis Sets<br>• Analyses<br>Section 7<br>Section 8<br>Section 9.1<br>Section 9.2.4.3<br>Section 9.2.4.4<br>Section 9.2.5<br>Section 9.3<br>Section 9.3.3<br>Section 9.4.1<br>Section 9.4.7<br>Section 9.5.1.2.1<br>Section 9.5.1.3.1<br>Section 9.5.1.3.2<br>Section 9.5.1.4.2<br>Section 9.5.1.5<br>Section 9.5.2<br>Section 9.5.4.1 |

**Revisions to Version 8.0**

**New version/date: Version 9.0/01 Feb 2017 (per Amendment 07)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | | Section 9.5.5<br>Section 9.7.1<br>Appendix 6 |
| Addition of the OLE Phase to evaluate the long-term safety and tolerability of elenbecestat (E2609) and cross reference to the detailed OLE Phase protocol in Appendix 6. | To add the OLE Phase in the context of the elenbecestat (E2609) clinical development program and study design to provide investigators with the location of the complete detailed OLE Phase protocol. | Section 7<br>Section 9.1<br>Section 9.1.3 |
| Addition of cross reference to objectives for OLE Phase protocol in Appendix 6. | To provide investigators with the location of the OLE Phase objectives. | Section 8 |
| Safety aspects have been built into the study design in light of the preclinical and clinical safety data with elenbecestat (E2609) to mitigate clinical risk are extended to the OLE Phase and 2 off-treatment Follow-Up Visits at 4 and 12 weeks after the last dose of study drug during the OLE Phase are added. | To provide instruction to investigators for continued monitoring procedures for mitigation of potential clinical risk associated with elenbecestat (E2609). | Section 9.2.5<br>Section 9.3.3<br>Section 9.5.1.5.7<br>Section 9.5.5 |
| Addition of requirement that subjects meet all inclusion criteria and not meet any of the exclusion criteria for the OLE Phase, with cross reference to the criteria for the OLE Phase in Appendix 6. | To provide investigators with the requirements for subject eligibility and the location of the OLE Phase inclusion and exclusion criteria. | Section 9.3 |
| Addition of cross reference to criteria for discontinuation of study drug during the OLE Phase in Appendix 6. | To provide investigators with the location of the criteria for discontinuation of study drug during the OLE Phase. | Section 9.3.3 |
| Prior and concomitant therapy restrictions are extended to the OLE Phase. | To provide instruction to investigators for prior and concomitant therapy during the OLE Phase. | Section 9.4.7 |
| Addition of cross reference to Table 14. | To direct the investigators to the detailed OLE Phase Schedule of Procedures/Assessments in | Section 9.5.1.2.1<br>Section 9.5.1.3.1 |

**Revisions to Version 8.0**

**New version/date: Version 9.0/01 Feb 2017 (per Amendment 07)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | Study 202: Open-label Extension Phase (Visit 21 through Visit 32). | Section 9.5.1.3.2<br>Section 9.5.1.4.2<br>Section 9.5.1.5<br>Section 9.5.1.5.1<br>Sections 9.5.1.5.3 to 9.5.1.5.11<br>Section 9.5.2<br>Section 9.5.5 |
| Addition of requirement to report all adverse events (AEs) observed during the OLE Phase; clarification that Visit 20 is the last visit for subjects who do not enter the OLE Phase and that Visit 34 is the last study visit for subjects who enter the OLE Phase. | Added for clarification. | Section 9.5.1.5.1 |
| Removed instructions for SAE reporting outside of the reporting period. | To match the standard template for SAE reporting. | Section 9.5.1.5.1 |
| Addition of ECG Assessments during the OLE Phase. | To specify that a single 12-lead ECG will be performed during the OLE Phase. | Section 9.5.1.5.6 |
| Addition of Dermatologic Assessments during the OLE Phase. | To stipulate that evaluation of skin assessments will be performed by the investigator during the OLE Phase. | Section 9.5.1.5.8 |

**Revisions to Version 8.0**

**New version/date: Version 9.0/01 Feb 2017 (per Amendment 07)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Addition of requirement to report all serious adverse events (SAEs) observed during the OLE Phase; clarification that Visit 20 is the last visit for subjects who do not enter the OLE Phase and that Visit 34 is the last study visit for subjects who enter the OLE Phase. | Added for clarification. | Section 9.5.4.1 |
| Addition of cross reference to Appendix 6 for discussion of OLE Phase statistical analyses. | To provide investigators the location of the OLE Phase statistical analyses discussion. | Section 9.7.1 |
| The term "total lymphocyte count" was changed to "absolute lymphocyte count". | To ensure consistency throughout the protocol and consistency with reports generated by the central laboratory. | Synopsis<br>• Concomitant Drug/Therapy<br>Section 9.2.5<br>Section 9.4.7<br>Section 9.5.1.5.3<br>Table 7<br>Appendix 2 |

**Revisions to Version 7.0**

**New version/date: Version 8.0/02 Nov 2016 (per Amendment 06)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Subjects currently receiving 5 or 15 mg elenbecestat (E2609) will be re-assigned to 50 mg elenbecestat (E2609) for the remainder of the double-blind treatment period provided they will receive at least 12 weeks of double-blind treatment after the re-assignment, (ie, no dose reassignments past Visit 17). | As elenbecestat (E2609) 50 mg has been selected as the appropriate dose for Phase 3 development, subjects should not continue with doses that are not being advanced clinically. Additionally, the re-assignment of subjects in elenbecestat (E2609) 5 and 15 mg to elenbecestat (E2609) 50 mg will further the safety and tolerability data in subjects exposed to elenbecestat (E2609) 50 mg. | Synopsis<br>• Study Design<br>• Number of Subjects<br>• Sample Size Rationale<br>Section 7.1<br>Section 9.1<br>Section 9.1.2.1<br>Section 9.4.1<br>Section 9.4.4<br>Section 9.5.2 |
| Clarified that one of the exploratory endpoints will analyze change from baseline in CSF amyloid and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment only. There will no analysis for treatment follow-up. | Correction | Synopsis<br>• Analysis for Exploratory Endpoints<br>• Exploratory Objective<br>Section 8.3<br>Section 9.7.1.1.3<br>Section 9.7.1.6.3 |
| The frequency of DSMB safety reviews after the 12-week interim safety analysis will be reassessed and details will be provided in the DSMB charter. | The DSMB charter will provide full details of interim safety reviews. | Synopsis<br>• Study Design<br>Section 9.1 |
| Removed the statement that subjects must be stable on acetylcholinesterase inhibitor (AChEI) or memantine to be included in the primary analyses. | This statement is no longer relevant as of Amendment 05. | Synopsis<br>• Concomitant Drug/Therapy<br>Section 9.4.7 |
| Added a statement to specify that additional analyses will be performed for subjects with dose re-assignment and details of these analyses and treatment group definitions will be provided in the statistical analysis plan (SAP); clarified that the SAP will be finalized before database lock. | To clarify that the SAP will be finalized prior to database lock and it will provide full details of the analyses to be performed for this study. | Section 9.7.1 |

**Revisions to Version 6.0**

**New version/date: Version 7.0/26 Sep 2016 (per Amendment 05)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Grammatical, typographical, and formatting changes | | Throughout |
| Removed Stage B from protocol. In line with this decision, the study objectives and endpoints have been modified and subjects who discontinue study drug early for any reason will no longer be required to complete efficacy visits after last dose of study drug. | This study will no longer be a Proof-of-Concept study. | Synopsis<br>• Study Protocol Title<br>• Investigators<br>• Sites<br>• Study Period and Phase of Development<br>• Objectives<br>• Study Design<br>• Early Discontinuation<br>• Number of Subjects<br>• Study Treatments<br>• Efficacy Assessments<br>• Safety Assessments<br>• Statistical Methods<br>• Study Endpoints<br>• Analysis Sets<br>• Efficacy and Biomarker Analyses<br>• Analysis for the Primary/Secondary/Exploratory Endpoints<br>• Pharmacokinetic Analyses<br>• Pharmacokinetic /Pharmacodynamic Analyses<br>• Interim Analyses<br>• Sample Size Rationale<br>Section 6<br>Section 7<br>Section 8<br>Section 8.3<br>Section 9.1<br>Section 9.2.1<br>Section 9.2.3<br>Section 9.2.4.4<br>Section 9.2.5<br>Section 9.3<br>Section 9.4.3 |

**Revisions to Version 6.0**

**New version/date: Version 7.0/26 Sep 2016 (per Amendment 05)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | | Section 9.4.4<br>Section 9.4.7<br>Section 9.2.5<br>Section 9.5.1.3.1<br>Section 9.5.1.4.2<br>Section 9.5.1.5.1<br>Section 9.5.2<br>Section 9.5.4.1<br>Section 9.5.5<br>Section 9.7<br>Section 10 |
| Updated Eisai contact information | Change in personnel and move to Building 100 | • Title Page<br>• Protocol Signature Page |

**Revisions to Version 5.0**

**New version/date: Version 6.0/29 Jun 2016 (per Amendment 04)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised number of investigational sites (from 40 to 35) | Feasibility | • Synopsis -<br>  • Study Design<br>  • Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Removed Exclusion Criterion No. 44 for male subjects regarding restrictions on child bearing | No longer a safety concern; E2609 has not shown a deleterious effect on sperm in preclinical reproductive toxicity studies. | • Synopsis:<br>  • Exclusion Criteria<br>• Section 9.3.2 |
| Added option for subjects who provided a CSF sample prior to randomization but who declined the CSF sample collection after 4 weeks of dosing to provide a postdose CSF sample at any point in the study (ie, even after 4 weeks of dosing). | Reflects the added value of CSF data for the PK/PD secondary objective of this study. In addition, given that PK steady state is achieved within the 1st 2 weeks of initiation of dosing, data collected post Week 4 visit is still considered to be applicable in assessment of the steady state effect. | • Synopsis -<br>  • Pharmacodynamic Assessments<br>• Section 5.3<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.5.1.3.3<br>• Section 9.5.1.4<br>• Table 6<br>• Table 7<br>• Table 8 |
| Revised details of restrictions to anticoagulant therapy and short-term steroid use revised/moved details regarding antiplatelet drugs to the main body of the protocol | To assist in subject recruitment and retention and considering that the strict restrictions were not necessary for subject safety | • Synopsis -<br>  • Concomitant Drug/Therapy<br>• Section 9.4.7<br>• Appendix 2 |
| Removed the >33% decrease from baseline for CD4, CD8, and CD19 as a trigger for more frequent testing of flow cytometry and CBCs. Additional safety monitoring for CD4, CD8, CD19, and CBCs will only be based on the population adjusted LLNs for clinically asymptomatic subjects. | Experience to date has indicated significant variability within the normal range, both for increases and decreases. Absolute counts of lymphocyte subsets are more meaningful than percentage decreases for triggering more frequent monitoring. | • Section 9.3.3<br>• Table 1<br>• Table 2 |

**Revisions to Version 5.0**

**New version/date: Version 6.0/29 Jun 2016 (per Amendment 04)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Added option to temporarily suspend study drug for subjects who are clinically asymptomatic but who meet CD4, CD8, or CD19 discontinuation thresholds on 2 consecutive tests. Introduce rules for ability to re-start study drug (ie, rechallenge) in these subjects. Only 1 cycle of temporary suspension and rechallenge with study drug permitted for any individual subject. | To assist in subject retention and to gain knowledge on the behavior of lymphocyte subsets on rechallenge. | • Section 9.3.3<br>• Table 1<br>• Table 2 |
| Added extra blood draw times with focus on lymphocyte subsets, CBCs, and immunoglobulins during the 12-week safety follow-up for all subjects. | To increase frequency of key safety monitoring parameters in post-treatment follow-up period so as to assess immunological changes after completion of study drug | • Synopsis<br>  • Study Design<br>  • Safety Assessments<br>• Section 9.1.2.2<br>• Section 9.1.2.3<br>• Section 9.2.5<br>• Section 9.3.3<br>• Table 7<br>• Table 8<br>• Section 9.5.1.5.7<br>• Section 9.5.5 |
| Clarified that the Functional Assessment Questionnaire is to be administered to the informant/caregiver, and not the subject. | Clarification | • Synopsis<br>  • Efficacy Assessments<br>• Section 9.5.1.3.1 |
| Added clarification that the Brief Smell Identification Test will be administered as part of the neurological examination | Clarification | • Synopsis<br>  • Safety Assessments<br>  • Interim Analyses<br>• Section 9.1.1.2<br>• Section 9.5.1.2.1<br>• Section 9.5.1.5.9<br>• Table 6<br>• Table 7 |

**Revisions to Version 5.0**

**New version/date: Version 6.0/29 Jun 2016 (per Amendment 04)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised number of randomized subjects in Stage A to n=60±20% | To allow for additional randomization based upon current number of subjects in screening at the time of amendment implementation | • Synopsis<br>  • Study Design<br>  • No. of Subjects<br>• Section 7<br>• Section 9.1<br>• Section 9.2.1<br>• Section 9.2.5<br>• Section 9.3<br>• Section 9.7.3 |
| Grammatical, typographical, and formatting corrections | Consistency | various |

**Revisions to Version 4.0**

**New version/date: Version 5.0, 06 Feb 2016 (per Amendment 03)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Add interim analyses of safety, and PK/PD data throughout Stage A | Decision making regarding the remainder of the study and the full elenbecestat (E2609) clinical development program | • Synopsis –<br>  • Exploratory Endpoint Analysis<br>  • Interim Analysis<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.4.6<br>• Section 9.7.1.7.1 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Grammatical, typographical, and formatting changes | | Throughout |
| Mandatory nature of CSF collection in study changed to voluntary. This change impacts the timing and details of the PK/PD interim analyses. It also impacts the nature of the CSF-related objectives, which will now be identified as exploratory. | To increase rate of subject consent into the study | • Synopsis –<br>  • Secondary Objectives<br>  • Exploratory Objectives<br>  • Study Design<br>  • Exclusion Criterion No. 12<br>  • Pharmacokinetic Assessments<br>  • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments<br>  • Safety Assessments<br>  • Secondary Endpoints<br>  • Exploratory Endpoints<br>  • Analysis for the Secondary Endpoints<br>  • Analysis for the Exploratory Endpoints<br>• Section 5.3<br>• Section 8.2<br>• Section 8.3<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.2.5<br>• Section 9.3.2<br>• Section 9.4.6<br>• Section 9.5.1.3.3<br>• Section 9.5.1.4<br>• Section 9.5.1.5.12<br>• Section 9.7.1.1.2<br>• Section 9.7.1.1.3<br>• Section 9.7.1.6.2<br>• Section 9.7.1.6.3<br>• Appendix 2, Listing 2 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Extended the range of cognitive impairment in delayed recall that would be considered inclusionary for the study and removed the eligibility nature of the cognitive tests repeated at the Baseline Visit. | Original delayed recall aspect of inclusion criterion #1 was considered to be too restrictive and was unnecessarily screening out subjects with MCI/prodromal AD. The eligibility nature of the cognitive tests repeated at the Baseline Visit has been removed in order to simplify the requirements of the pretreatment period for the study. | • Synopsis –<br>  • Inclusion/ Exclusion Criteria<br>• Section 9.3.1<br>• Section 9.3.2 |
| Addition of historical amyloid PET scans for determination of eligibility for the study. Subjects with historical PET scans will not be part of the longitudinal PET analyses and therefore will not require a second PET scan at either Visit 18 or ED. | To provide the sites with greater operational flexibility and reduce subject burden. | • Synopsis –<br>  • Inclusion/Exclusion<br>  • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments<br>• Section 9.1.1<br>• Section 9.2.4.3<br>• Section 9.3.1<br>• Section 9.5.2<br>• Table 6<br>• Table 7 |
| Added the need for safety laboratory tests to be repeated for subjects whose pre-treatment period is extended due to active infection. | To ensure that all baseline safety laboratory tests are repeated for subjects whose pretreatment period is extended. | • Synopsis –<br>  • Inclusion/Exclusion<br>• Section 9.3.2<br>• Section 9.5.2<br>• Table 6 |
| Clarified that exclusion criterion No. 22 (exclusion of subjects with CD4, CD8, or CD19 absolute counts below the LLN) applies to flow cytometry tests conducted at both the Screening and the Baseline Visits. Furthermore, LLNs that are adjusted for the subject population under study will be used. | It was not clear that Exclusion Criterion No. 22 applied to both the Screening and the Baseline Visits. The LLNs for CD4, CD8 and CD19 absolute counts require adjustment for the age of the patient population in this study. | • Synopsis –<br>  • Inclusion/ Exclusion Criteria<br>• Section 9.3.2 |
| Provided additional detail | Added to provide clarity | • Synopsis – |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| regarding scope of Exclusion Criterion No. 34 which excludes subjects with hypopigmentation conditions. | for the sites. | • Exclusion Criteria<br>• Section 9.3.2 |
| Revised number of clinical sites from 30 to 40 | For feasibility purposes | • Synopsis –<br>• Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Relaxed the requirement for the cognitive assessments at Screening Visit 1 to be conducted in a certain order and revised the recommended order in which the assessments could be conducted. | To provide the sites with greater operational flexibility. | • Section 9.1.1<br>• Figure 2<br>• Section 9.5.1.3.1<br>• Section 9.5.2<br>• Table 6 |
| Clarify the duration for which the Safety magnetic resonance imaging (MRI) scan, the amyloid PET scan and the lumbar puncture (LP) collected CSF conducted at Screening are considered valid. | To provide sites with greater operational flexibility, particularly for re-screening of screen fail subjects. | • Section 9.1.1 |
| Clarify that for subjects meeting criteria for weekly monitoring of lymphocyte subsets, these can be accommodated within the scheduled clinic visits during the early stages of the treatment period of the study. | To provide operational clarity to the sites. | • Synopsis –<br>• Exclusion Criteria<br>• Section 9.3.2<br>• Section 9.3.3<br>• Section 9.5.1.5.3 |
| Added the requirement for complete blood counts (CBC) with differentials to be performed whenever repeat or unscheduled flow cytometry tests are performed. | Such that CBC data are available at all times when flow cytometry data is available. | • Section 9.3.3<br>• Table 1<br>• Section 9.5.2<br>• Table 6<br>• Table 7 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Added 30-day window to the duration of the pre-treatment period if required for medical or operational reasons. | To provide the sites with greater operational flexibility. | • Synopsis –<br>  • Study Design<br>  • Duration of Treatment<br>• Section 9.1<br>• Figure 1<br>• Section 9.1.1<br>• Section 9.1.1.2<br>• Section 9.5.2<br>• Table 6 |
| Clarified the timing of the start of the Randomization Phase | Clarification | • Section 9.1.1<br>• Section 9.1.2<br>• Section 9.5.2<br>• Table 6<br>• Table 7 |
| Increased number of MCI/Prodromal or mild to moderate AD subjects screened for entry into the study | To reflect the higher screen failure rate than originally anticipated | • Synopsis –<br>  • Number of Subjects |
| Removal of CD127 cell surface markers | FoxP3 is the most accepted marker to measure T regulatory cells and additional assessment of CD127 is not required. | • Section 9.5.1.5.3<br>• Table 4<br>• Section 9.5.2.1 |
| Made the clinical biochemistry, urinalysis, CBC, lymphocyte subsets, and immunoglobulin tests mandatory at Visit 20, regardless of clinical significance at Visit 19. | For more comprehensive safety data at the second follow-up visit. | • Section 9.5.2<br>• Table 7 |
| Corrected reference to Exclusion Criterion No. 20 (and not to Exclusion #19) in footnote to Table 6 and Table 7 regarding timing of Visit 3 in relation to Visit 2. | Correction | • Section 9.5.2<br>• Table 6<br>• Table 7 |
| Revised details regarding prohibited antiplatelet drugs | To distinguish between those subjects who consent to CSF sample collection and those who do not | • Appendix 2, Listing 2 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015 (per Amendment 01)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised inclusion to allow for enrollment of mild to moderate AD subjects in Stage A and expand the Stage B mild AD cohort to also include moderate AD subjects | To collect safety data in a wider range of AD patients. | • Title Page<br>• Synopsis –<br>  • Objectives<br>  • Study Design<br>  • Number of Subjects<br>  • Inclusion/Exclusion Criteria<br>  • Study Treatments<br>  • Efficacy Assessments<br>  • Study Endpoints<br>  • Efficacy Analyses<br>  • Interim Analyses<br>  • Adaptive Randomization<br>  • Sample Size<br>• Section 5.3<br>• Section 7<br>• Section 8 (and all subsections)<br>• Section 9.1<br>• Section 9.1.1<br>• Figure 1<br>• Section 9.2.1<br>• Section 9.2.2<br>• Section 9.2.3<br>• Section 9.2.4.3<br>• Section 9.2.4.4<br>• Section 9.3<br>• Section 9.3.1<br>• Section 9.3.2<br>• Section 9.4.1<br>• Section 9.4.3<br>• Section 9.4.4<br>• Section 9.5.1.3.1<br>• Section 9.7.1.1.2<br>• Section 9.7.1.1.3<br>• Section 9.7.1.4<br>• Section 9.7.1.6<br>• Section 9.7.1.6.2<br>• Section 9.7.1.6.3<br>• Section 9.7.1.8.2<br>• Section 9.7.3<br>• Section 9.7.4 |
| Revised inclusion criteria for MMSE to ≥16 from ≥20 | The MMSE score is used as a cut-off for the most impaired subject that would be eligible for the study. Lowering the MMSE inclusion from ≥20 to ≥16 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD | • Synopsis –<br>  • Inclusion/Exclusion Criteria<br>• Section 9.3.1 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015 (per Amendment 01)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | cohort. | |
| Revised inclusion criteria for FAQ to ≤24 from ≤20 | As for the MMSE, the FAQ score is used as a cut-off for the most impaired subject that would be eligible for the study. Revising the FAQ inclusion from ≤20 to ≤24 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD cohort, and is consistent with an MMSE inclusion of ≥16. | • Synopsis –<br>  • Inclusion/Exclusion Criteria<br>• Section 9.3.1 |
| Revised exclusion criteria such that small arachnoid cysts are not necessarily exclusionary | Arachnoid cysts are a common finding in otherwise healthy subjects. Small lesions (<1 cm in diameter) are generally not considered clinically significant and if discovered incidentally no long term follow up is routinely required. | • Synopsis –<br>  • Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised exclusion criteria for Ig (IgG, IgA, or IgM) to specify that levels below the LLN at Screening or Baseline need not be exclusionary | For subjects with a Screening or Baseline IG level <LLN to be considered for continuation in the study, assessment of clinical significance of the finding will be required. A finding of "not clinically significant" must be agreed between the Investigator and Medical Monitor in order for the subject to continue in the study. | • Synopsis –<br>  • Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised text to provide instructions for subject assent and associated consent by a legal representative for subjects who the Investigator considers not to have the capacity to consent themselves | With the expansion of the patient population to include moderately demented subjects, it was necessary to provide directions regarding the consenting process for subjects considered to be lacking the capacity to consent themselves. | • Section 5.3 |
| Revised number of clinical sites to 30 from 25 | For feasibility purposes. | • Synopsis –<br>  • Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015 (per Amendment 01)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Added allowance for Tier 1 and Tier 2 screening assessments to be performed on the same day | Added to provide operational clarity for the sites. | • Section 9.1.1.1<br>• Table 6 |
| Removed requirements for MRIs to include sequences for resting state functional MRI | This was an error and should not have been included in the original protocol. | • Table 6<br>• Table 7 |
| Revised text to clarify that on visits where CSF collection takes place, the CSF collection need not take place on the same day as the cognitive testing for that visit | Added to provide operational clarity for the sites. | • Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised text to clarify that the most important efficacy assessment to keep blinded from safety data is the CDR. | Added to provide operational clarity for the sites. | • Synopsis –<br>  • Safety Assessments<br>• Section 9.4.6<br>• Section 9.5.1.5 |
| Revised text to allow PK blood sample and PD blood samples to be taken either shortly before or shortly after the LP on CSF days | Added to provide operational flexibility for the sites. | • Section 9.5.1.4.1<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised Sponsors Grading for Laboratory Values for the following analytes: lymphocytes, neutrophils, albumin, creatinine, phosphate, and potassium serum-high (hyperkalemia) | Corrections made to align with the values for grading used by the central clinical laboratory for this study. | • Appendix 1 |
| Revised details regarding prohibited antiplatelet drugs | Previous version incorrectly referenced a biomarker subgroup. All subjects in this study will need to provide CSF samples. | • Appendix 2; Listing 2 |
| Revised grammar, spelling, etc. | Compliance with current company style guide and for general consistency. | Throughout protocol |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revisions to grammar, spelling, etc. | Compliance with current company style guide and for general consistency | • Throughout protocol |
| Revisions made per new company protocol template | Alignment with current Eisai template | • Synopsis –<br>  • Inclusion/Exclusion Criteria<br>• Section 9.1.2.3<br>• Section 9.3.1<br>• Section 9.3.2<br>• Section 9.5 (related subsections)<br>• Section 9.5.4<br>• Section 9.5.4.1<br>• Section 9.5.4.2<br>• Section 9.5.4.3 |
| Clarified classification of MCI due to AD | Clarification that MCI due to AD population will also be consistent with the research criteria for Prodromal AD in that impaired episodic memory is required and will be tested using a list learning task (the International Shopping List Task) | • Synopsis –<br>  • Study Design<br>• Section 9.1 |
| Replaced "enroll" with "randomize," pertaining to subject entry into study | Correction to terminology | • Synopsis –<br>  • Study Design<br>• Section 9.1<br>• Section 9.3 |
| Added criterion excluding subjects with hepatic impairment and total bilirubin greater than 1.5×ULN or INR greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded. | At request of FDA, exclude subjects who have hepatic impairment | • Synopsis –<br>  • Inclusion/Exclusion Criteria<br>• Abbreviation List<br>• Section 9.3.2 |
| Added coagulation parameters for prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR) to screening and baseline procedures | Screen for hepatic impairment | • Synopsis –<br>  • Inclusion/Exclusion Criteria<br>• Abbreviation list<br>• Section 9.3.2<br>• Table 4<br>• Table 6<br>• Table 8 |
| For subjects who discontinue study drug prematurely, conduct efficacy assessments postdose at same time points as subjects who continue in the study. Added FAQ to this set | To facilitate efficacy analyses, which are based on longitudinal modeling for all subjects | • Synopsis –<br>  • Study Design<br>• Section 9.1.2.2<br>• Section 9.3.3<br>• Section 9.5.4.1 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| of efficacy assessments. | | • Section 9.5.5<br>• Table 7 |
| Delete diagram of E2609 structure | This display is not needed for the protocol. The Investigator's Brochure has this information. | • Section 9.4.2.1 |
| Additional blood samples to be taken at Visits 19 and 20 | Samples are to be put in storage to allow for assessment of immune status at end of study, as needed. | • Synopsis –<br>  • Assessments<br>• Table 8 |
| Add subheadings to Section 9.7 describing the primary endpoint analysis, and text clarifying that no multiplicity adjustments will be done to account for the interim analyses | To distinguish clearly the primary analysis and the sensitivity analyses of the primary endpoint | • Synopsis –<br>  • Efficacy Analyses<br>• Section 9.7.1.6.1 |
| Clarification of PK sampling upon Early Discontinuation | Additional operational details of the timing of the PK sampling at the ED visit provided | • Section 9.5.1.4.1<br>• Table 7 |
| Clarification of ApoE testing | Clarification that the ApoE genetic testing will be for homozygous or heterozygous E4, versus non-E4 | • Section 9.5.1.4.2 |
| Revision to PK/PD interim analysis text | Confirm that interim PK/PD analysis will be conducted by an independent group | • Section 9.4.6 |
| Addition of text regarding safety signals with E2609 | To provide information on safety-driven dose adjustments | • Synopsis –<br>  • Study Design<br>• Section 9.1 |
| Addition of PBMC collection/assessment at Baseline, during treatment, and post-treatment | Recent animal studies have shown an effect of E2609 on this model so they will be added to the 202 clinical study as an additional exploratory assessment. | • Synopsis –<br>  • Safety Assessments<br>• Section 9.2.5<br>• Section 9.5.1.5<br>• Table 4<br>• Table 6<br>• Table 7<br>• Table 8 |
| Stipulate that exploratory biomarker analyses may be conducted using blood or CSF samples that may have been drawn for other purposes | To allow more flexibility for possible exploratory biomarker studies associated with study drug or disease, including miRNA and DNA | • Synopsis –<br>  • Assessments<br>• Abbreviation list<br>• Section 9.5.1.4.2<br>• Section 9.5.1.5.12<br>• Table 6<br>• Table 7 |
| Prohibit concomitant medications that are strong CYP3A4, inhibitors, but clarify that no restrictions are needed for other CYP3A4 | At request of FDA, in light of finding that inhibition of CYP3A4 by a reference agent increases plasma levels of E2609 | • Synopsis –<br>  • Concomitant Drug/Therapy<br>• Section 7.1 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| inhibitors, CYP3A4 inducers, or CES2 inhibitors | | • Section 9.4.7<br>• Appendix 2, Listing 6 |
| Addition of tests for viral characterization at Baseline | To confirm by serology information of subjects prior exposure to common viruses pre-dosing with study drug | • Section 9.5.1.2.2<br>• Table 4<br>• Table 6<br>• Table 8 |
| Use of a centralized dermatologist assessment via photography | A centralized approach, using standardized photography, to FDA-required serial dermatological assessments will be employed for consistency of assessments between sites and for consistency of longitudinal assessments of individual subjects. | • Synopsis –<br>  • Safety Assessments<br>• Section 9.2.5<br>• Section 9.5.1.5<br>• Section 9.5.1.5.8<br>• Table 6<br>• Table 7 |
| Removal of testing for benzodiazepines or opioids as part exclusion criteria #35 | To differentiate appropriate medicinal use from recreational drug use or abuse | • Synopsis –<br>  • Exclusion Criteria<br>• Section 9.3.2 |
| Addition of analysis of other covariates such as adjusted hippocampal volume will be studied | Hippocampal volume has been shown to correlate with rate of cognitive decline and as such is a key covariate to be used in the analyses. | • Synopsis –<br>  • Analysis of Primary Endpoint<br>• Section 9.7.1.6.1 |
| Addition of clarifications to ophthalmic examination | To provide more detail around the requirements for the ophthalmic exam | • Synopsis –<br>  • Safety Assessments<br>• Section 9.5.1.5.13<br>• Table 6<br>• Table 7 |
| Addition of details regarding specific method of CSF collection (ie, gravity drip) | Use of materials required for suction method when collecting CSF can affect the PD data and so it is important to make it clear that only the gravity drip method can be used for collecting CSF in this study for protecting the quality and the consistency of the CSF PD data. | • Section 9.5.1.3.3<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Addition of specific testing for B12 levels at Screening | Abnormally low serum vitamin B12 levels are exclusionary for the study (exclusion criterion 8) but a blood draw for Vitamin B12 was inadvertently missed out of Table 6 in protocol version 1. | • Synopsis –<br>  • Exclusion Criteria<br>• Section 9.3.2<br>• Section 9.5.1.2.3<br>• Figure 2<br>• Table 6 |
| Addition of details regard AEs that might be signals of possible drug abuse potential | Changed terminology re: collection of additional information for AEs that might be signals of possible abuse potential. No longer use the | • Synopsis –<br>  • Safety Assessments<br>• Section 9.2.5<br>• Section 9.5.1.5.1 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | word "narrative" in order to avoid potential confusion with standard clinical trial narratives eg, for serious adverse events, adverse events leading to withdrawal, etc. | • Appendix 4 |
| Addition of clarification regarding position for taking vital signs (ie, supine) | The American Heart Association guidelines only mention supine, standing, and sitting as positions for taking HR and BP measurements. Therefore, have changed required position from semi-supine to sitting. | • Section 9.5.1.5.4<br>• Table 6<br>• Table 7 |
| Stipulated that study drugs are to be taken with food | For consistency of treatment conditions | • Section 9.5.1.4.1 |
| Change to list of Study Specific AEs which should be considered SAEs | Eisai's standard procedures have changed such that non-serious study specific adverse events of interest are no longer reported to Eisai Product Safety; instead, any additional information required for such non-serious adverse events will be obtained through other methods. In addition, certain events (new onset seizures, ocular herpes) are now to be classified as serious as important medical events, regardless of whether they meet standard ICH serious criteria. | • Section 9.5.1.5.1<br>• Section 9.5.1.5.2 |
| Increased blood volume for PK | To match collection tubes and ensure sufficient sample for planned assays | • Table 8 |
| Corrected error in definition of PK analysis set | For accuracy | • Synopsis –<br>  • Study Endpoints<br>• Section 9.7.1.2 |
| Addition of details regarding discontinuation of study drug | To clearly and consistently differentiate "discontinuation from study drug" from "withdrawal from study" | • Synopsis<br>• Section 7<br>• Section 9.1.2.1<br>• Section 9.2.5<br>• Section 9.3.3<br>• Table 1<br>• Table 2<br>• Section 9.4.1<br>• Section 9.4.4<br>• Section 9.5.1.5.1<br>• Section 9.5.1.5.3<br>• Section 9.5.5 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Re-ordered prohibited medication lists | For consistency, all lists re-ordered in alphabetical order of generic drug name, and footnotes revised for overall consistency | • Appendix 2 |
| Moved nefazodone from Listing 9 to Listing 6 | Nefazodone is a strong CYP3A4 inhibitor and is therefore prohibited. | • Appendix 2 |

# 1 TITLE PAGE


## Clinical Study Protocol

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of Elenbecestat (E2609) in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01 and 05) |

| **Sponsor:** | Eisai Inc. | Eisai Ltd. | Eisai Co., Ltd. |
|---|---|---|---|
| | 100 Tice Boulevard | European Knowledge Centre | 4-6-10 Koishikawa |
| | Woodcliff Lake, | Mosquito Way | Bunkyo-Ku, |
| | New Jersey 07677 | Hatfield, Hertfordshire | Tokyo 112 8088 |
| | United States | AL10 9SN United Kingdom | Japan |

| | | |
|---|---|---|
| **Investigational Product Name:** | Elenbecestat (E2609) | |
| **Indication:** | Alzheimer's disease | |
| **Phase:** | 2 | |
| **Approval Date:** | V1.0 | 15 Jul 2014 (original protocol) |
| | V2.0 | 21 Oct 2014 (revised original protocol) |
| | V3.0 | 28 May 2015 (Amendment 01) |
| | V4.0 | 05 Nov 2015 (Amendment 02) |
| | V5.0 | 06 Feb 2016 (Amendment 03) |
| | V6.0 | 29 Jun 2016 (Amendment 04) |
| | V7.0 | 26 Sep 2016 (Amendment 05) |
| | V8.0 | 02 Nov 2016 (Amendment 06) |
| | V9.0 | 01 Feb 2017 (Amendment 07) |
| | V10.0 | 10 Dec 2018 (Amendment 08) |
| **IND Number:** | 109308 | |
| **EudraCT Number:** | 2014-002723-94 | |

**GCP Statement:** This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local GCP and regulations. All required study documentation will be archived as required by regulatory authorities.

**Confidentiality Statement:**

This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

# 2 CLINICAL PROTOCOL SYNOPSIS

**Compound No.:**
E2609

**Name of Active Ingredient:**
*N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

**Study Protocol Title**
A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of Elenbecestat (E2609) in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01 and 05)

**Investigators**
Investigators in the United States only (revised per Amendment 05)

**Sites**
Approximately 35 sites, United States only (revised per Amendments 01, 02, 04, and 05)

**Study Period and Phase of Development** (revised per Amendment 07)

This Phase 2 study will include the following:

- Core Study: approximately 32 months including the Prerandomization and Randomization Phases (revised per Amendments 05 and 07)
- Open-label Extension (OLE) Phase: approximately 51 months including 48 months of Treatment Period and 3 months of off-treatment Follow-up Period (revised per Amendments 07 and 08)

**Objectives**

**Core Study** (revised per Amendment 07)

**Primary Objective** (revised per Amendment 05)

To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with elenbecestat in Mild Cognitive Impairment (MCI)/Prodromal subjects and in subjects with Mild to Moderate Dementia due to Alzheimer's Disease (referred to as mild to moderate AD throughout the protocol) (revised per Amendments 01 and 07)

**Secondary Objectives** (revised per Amendments 02 and 05)

- To characterize the plasma and cerebrospinal fluid (CSF) pharmacokinetics (PK) of elenbecestat
- To assess the effects of elenbecestat on Aβ(1-x) and Aβ(1-42) in CSF from 4 weeks and up to 18 months of treatment

**Exploratory Objectives** (revised per Amendments 01, 02, 04, and 05)

- To explore the effects of elenbecestat on CSF Aβ(1-40) and beta (β)-amyloid converting enzyme 1 (BACE1) measurements from 4 weeks and up to 18 months of treatment
- To explore the effects of elenbecestat compared with placebo on various biomarkers.

Biomarkers to be explored may include but are not limited to:

a. CSF biomarkers of neurodegeneration (eg, total tau [t-tau], phosphorylated-tau [p-tau]) after 18 months of treatment
b. Plasma and CSF amyloid, and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment (revised per Amendment 06)
c. Total hippocampal atrophy at 12 and 18 months of treatment, as measured by volumetric magnetic resonance imaging (vMRI)
d. vMRI measurements including left and right hippocampal volume, whole brain volume and total ventricular volume at 6, 12, and 18 months of treatment
e. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)

- To explore the effects of elenbecestat compared with placebo on clinical status at various time points during 18 months of treatment, and during posttreatment follow-up, by assessment of:
  a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog14)
  b. The Clinical Dementia Rating (CDR) scale
  c. The Mini-Mental State Examination (MMSE)
  d. The International Shopping List Task (ISLT)
  e. The CogState Brief Battery (CBB)
  f. The Functional Assessment Questionnaire (FAQ; also known as the Functional Activities Questionnaire)
- To explore the relationship between the treatment effects of elenbecestat on measured clinical efficacy scales (eg, MMSE, CDR) and its effects on CSF amyloid, CSF amyloid isoforms, brain amyloid, and vMRI
- To explore relationships between both elenbecestat dose and exposure, with pharmacodynamic (PD) and safety endpoints

**Open-Label Extension Phase** (revised per Amendments 07 and 08)

**Primary Objective:**

- To assess the long-term safety and tolerability of daily dosing with elenbecestat 50 mg in MCI/Prodromal subjects and in subjects with Mild to Moderate Dementia due to AD

**Secondary Objectives**

- To explore the long-term effects of elenbecestat on clinical status by assessment of:
  a. The MMSE
  b. The FAQ
- To explore the long-term effects of elenbecestat on:
  a. vMRI including, but not limited to, total hippocampal volume, left and right hippocampal volume, whole brain volume, and total ventricular volume with up to 24 and 48 months of treatment in the Extension Phase.
  b. Plasma amyloid at 12, 24, 36, and 48 months of treatment in the Extension Phase.

**Study Design**

This will be a multicenter, placebo-controlled, double-blind, parallel-group, randomized, dose-finding

study with an open-label Extension Phase of up to 51 months in subjects with MCI/Prodromal AD or mild to moderate AD. (revised per Amendment 07) A common set of inclusion criteria, consistent with the National Institute on Aging–Alzheimer's Association (NIA-AA) clinical research criteria for MCI due to Alzheimer's disease (AD) or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with the criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study consists of 3 phases: Prerandomization, Randomization, and open–label Extension Phase. The Prerandomization and Randomization Phases are referred to as the Core Study throughout the protocol. (revised per Amendment 07)

**Core Study**

The Prerandomization Phase (up to 60 days, plus an additional window of up to 30 days if required [revised per Amendment 02]) includes a Screening Visit (Visit 1) and a Baseline Visit (Visit 2). All screening assessments (within 4 distinct tiers) must be completed, and eligibility to continue in the study confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-up (post last dose; 12 weeks).

The study will be limited to approximately 35 sites in the United States. (revised per Amendments 01, 02, and 04) Subjects will initially be randomized 1:1:1:1 to 4 treatment groups (5, 15, or 50 mg elenbecestat [E2609] or placebo) within each of the 2 clinical populations. (revised per Amendments 01, 04, 05, and 06) In addition to the placebo group, 3 elenbecestat doses will be used to reduce CSF amyloid β levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/PD modeling has shown that these doses should achieve these targets when administered once daily (QD) with food, and these doses will be evaluated based on the 4-week (or later) assessment of CSF Aβ(1-x) from subjects who provide voluntary consent for CSF measurement. (revised per Amendment 02) Upon implementation of Amendment 06, at the next regularly scheduled visit, subjects receiving elenbecestat 5 or 15 mg who have not yet completed Visit 17 (Week 66), will be re-assigned in a blinded manner to elenbecestat 50 mg for the remainder of the double-blind Treatment Period. In order to maintain the blind, all subjects who have not yet had Visit 17 will go through the same procedures with the placebo-randomized subjects continuing to receive placebo and those randomized to elenbecestat 50 mg continuing to receive 50 mg. (revised per Amendment 06)

Safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the 1st subject is randomized into the study through the time the last subject is randomized, an independent data safety monitoring board (DSMB; including at least 1 immunologist) will review all safety data in an unblinded manner. (revised per Amendment 06) The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. (revised per Amendments 01, 04, and 05)

Interim analyses of the elenbecestat plasma PK for all subjects and the elenbecestat CSF PK and PD profiles will be performed on baseline data and samples collected after at least 4 weeks of treatment. (revised per Amendment 05) These interim analyses, as well as analyses of safety data, will be performed on an ongoing basis throughout the study. Refer to the Interim Analysis section for more detail. These data will be used to evaluate the CSF PD effects of elenbecestat doses, where PD is

measured as reductions from baseline in CSF Aβ(1-x) levels. (revised per Amendments 01 and 02) The median and mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks or more of treatment for each dose of elenbecestat and the 90% CI for the median will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data and will relate the average steady state plasma concentration of elenbecestat to CSF Aβ(1-x) percentage reduction from baseline determined after at least 4 weeks of dosing. (revised per Amendments 01, 02, 03, 04, and 05)

Once subjects have completed at least 12 weeks of treatment (or discontinued study drug early) an interim safety analysis will be conducted by Eisai and the DSMB. At the completion of this interim safety review, the frequency of subsequent unblinded safety reviews will be re-evaluated by the DSMB and the sponsor and this information will be provided in the DSMB charter. (revised per Amendment 06) Subjects will continue study drug while the DSMB reviews all the available safety data. (revised per Amendments 01, 04, 05, and 06).

**Open-Label Extension Phase** (revised per Amendments 07 and 08)

The Extension Phase allows eligible subjects to receive elenbecestat 50 mg daily for up to 48 months (4 years).

All subjects who complete 18 months of treatment and 12 weeks of follow-up in the Core Study and who satisfy the entry criteria for the Extension Phase are eligible to enter the Extension Phase. After completing all Visit 20 procedures in the Core Study Follow-Up Period, eligible subjects will have the option to participate in the Extension Phase within 4 weeks of Visit 20 of the Core Study. These subjects may transition to the Extension Phase immediately following Visit 20 (on the same day) if the decision to proceed with the Extension Phase has been made at that time. The medical monitor must be contacted if Visit 21 is to occur more than 4 weeks after Visit 20.

For all subjects, assessments performed at Visit 20 may serve as Visit 21 (start of the Extension Phase) results with the following exceptions: laboratory assessments and vital signs must be repeated if Visit 21 occurs more than 10 days from Visit 20.

Subjects who are eligible and who consent to participate in the Extension Phase will be administered elenbecestat 50 mg daily at Visit 21. Subjects with pending INR and serum pregnancy test results (females subjects of child bearing potential only) but who are otherwise eligible may begin Extension Phase dosing at Visit 21; however, these subjects must discontinue study drug treatment immediately if either test result meet the exclusion criteria.

During the Extension Phase, safety assessments will continue to be monitored and all AEs and SAEs will be recorded. Vital signs, hematology, blood chemistry, and urine values will be monitored at every scheduled visit. Clinical assessments (MMSE and FAQ) will be administered every 3 months for the first 24 months and every 4 months thereafter. Blood for PD analyses will be collected every 12 months. All subjects will be assessed using safety MRIs and vMRI measurements at 24 and 48 months. Subjects who discontinue early from the Extension Phase will have safety brain MRI and vMRI assessments at the Early Discontinuation (ED) Visit if these assessments have not already been performed during the preceding 90 days. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. (revised per Amendment 08)

**Early Discontinuation (Core Study)**

Subjects who prematurely discontinue taking study drug prematurely for any reason during the Core Study will undergo an ED Visit within 7 days of their last dose of study drug. Follow-up Visits will also be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug. (revised per Amendments 04 and 05)

**Follow-Up (Core Study)**

All subjects, regardless of whether they complete all 18 months of treatment or prematurely discontinue study drug, will complete 4 post-treatment Follow-up Visits: 2, 4, 8, and 12 weeks after the last dose of study drug. If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled (UNS) Visits during the post-treatment Follow-up Period. (revised per Amendment 04)

**Early Discontinuation** (**Open-Label Extension Phase)** (revised per Amendment 07)

Subjects who prematurely discontinue study drug for any reason during the Extension Phase will undergo an ED Visit within 7 days of their last dose of study drug. Follow-up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug.

**Follow-Up (Extension Phase)** (revised per Amendments 07 and 08)

All subjects, regardless of whether they complete all 48 months of treatment in the Extension Phase or prematurely discontinue study drug, will complete 2 posttreatment Follow-up Visits at 4 and 12 weeks after the last dose of study drug. (revised per Amendment 07) If clinically indicated, more frequent safety assessments can be conducted as part of UNS visits during the Extension Phase Follow-up Period.

**Number of Subjects**

Approximately 400 MCI/Prodromal or mild to moderate AD subjects will be screened to provide approximately 60 (±20%) randomized subjects (with a target of approximately 15 subjects per treatment arm). There will be no limit to the number of subjects randomized from either clinical cohort. (revised per Amendments 01, 02, 04, and 05)

**Inclusion Criteria**

**Core Study**

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD or AD dementia and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at Screening Visit 1:**
(revised per Amendment 02)

a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, caregiver or informant, or clinician's observation
b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT. Alternatively, cognitive impairment of at least 0.5 SD from age-adjusted norms in delayed recall on the ISLT plus impairment of at least 1 SD from age-adjusted norms in at least 1 other computerized learning and memory test (ISLT immediate recall, or 1 of the learning and memory components of the CBB). (revised per Amendment 02)
c. FAQ ≤24 (revised per Amendment 01)

d. MMSE ≥16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading; an historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group (revised per Amendment 02)
3. Male or female, age 50 to 85 years, inclusive at time of consent
4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.
5. If receiving acetylcholinesterase inhibitors (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.
6. Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization.

**Extension Phase** (revised per Amendment 07)

1. Subjects who complete the 18-month treatment and the 12-week Follow-up Period (Visit 20) in the Core Study and whose Visit 20 falls within a 4-week window from the start of the Extension Phase (Visit 21). Permission must be obtained from the medical monitor if Visit 21 is to occur more than 4 weeks from Visit 20.
2. Subjects must continue to have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the Extension Phase.

**Exclusion Criteria (revised per Amendment 04)**

**Core Study**

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or magnetic resonance imaging (MRI)
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to

be due to seizures within 5 years of Screening.

5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and <1 cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could, in the opinion of the investigator, confound the MCI/Prodromal or mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendments 01 and 02)
7. A score of ≥8 on the 15-item Geriatric Depression Scale at Screening
8. Abnormally low serum vitamin B12 (<lower limit of normal [LLN]) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the lower limit of normal (LLN) for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
12. Any contraindications to lumbar puncture (LP) for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity). Only applicable to subjects consenting to CSF sample collection (revised per Amendment 02)
13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection

19. Any live vaccine in the 3 months before randomization
20. Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below population-adjusted LLN at Screening or Baseline and confirmed by a repeat test conducted 1 week after the initial test. The population-adjusted LLN for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are 396, 157, and 74 cells/μL respectively. (revised per Amendment 02)
23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the investigator and the medical monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of clinical immunodeficiency. The discussion with the medical monitor should include a detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)
24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate ECGs. A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute at Screening or Baseline
29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell

carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.

33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo). Diagnosis of an underlying disease causing hypopigmentation is not necessary for exclusion if the clinical presentation is consistent with such a condition. Hypopigmentation associated with scarring need not be exclusionary. (revised per Amendment 02)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the 1st dose of study drug.
43. Females of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized

partner with confirmed azoospermia) throughout the entire study treatment period and for 28 days after study drug discontinuation.

b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.

c. Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
(NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

**Extension Phase** (revised per Amendment 07)

1. Subjects who discontinue study drug prematurely during the Core Study are not eligible to participate in the Extension Phase.
2. Subjects with any active infection within 4 weeks of Visit 21.
3. Subjects with absolute lymphocyte count below the LLN within 10 days of Visit 21.
4. Subjects who develop the following conditions from the time of screening for the Core Study to the start of the Extension Phase:

    a. Hepatic impairment, with total bilirubin greater than 1.5×ULN or INR greater than 1.7. Subjects with Gilbert's syndrome need not be excluded on the basis of an elevated bilirubin, provided that they have no other signs or symptoms suggestive of hepatic impairment

    b. Any contraindications to MRI scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners)

    c. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately

    d. Immunoglobulin (Ig) deficiency or other immunodeficiency disorders

    e. Chronic viral hepatitis

    f. TB

    g. Ophthalmic shingles

    h. Ocular HSV infection

    i. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:

        - Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded
        - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded

- Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted)

j. Malignant neoplasms (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject from the Extension Phase).

5. Subjects with prolonged QTcF interval at Visit 20 or Visit 21. Subjects with a single 12-lead ECG QTcF >450 msec should have 2 additional ECGs performed at least 1 min apart and the mean QTcF from the triplicate ECGs should be calculated. Subjects with a mean QTcF value >450 msec are not eligible to enter the Extension Phase.
6. Subjects with significant pathological findings on brain MRI including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).
7. Subjects who have a "yes" answer to the C-SSRS suicidal ideation questions 4 or 5 at Visit 20 or Visit 21 or any suicidal behavior during the study before the start of the Extension Phase.
8. Female subjects of child bearing potential who meet any of the follow criteria:
    a. Do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period and for 28 days after study drug discontinuation
    b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation
    c. Who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
9. Females who are lactating or pregnant (as documented by a positive β-hCG or hCG test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Visit 20 or Visit 21.
10. Subjects with medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments.
11. Any other clinically significant abnormal findings in vital signs, ECGs, and laboratory tests that would, in the investigator's opinion, would affect the subject's safety or interfere with study assessments during the Extension Phase.

**Study Treatments (Core Study)**

Elenbecestat (E2609) tablets of 5-, 10-, and 25-mg dose strengths will be supplied. Placebo tablets to match elenbecestat will be of identical appearance. Each subject will receive 2 tablets, which when combined will make up the required doses of elenbecestat or placebo, to be administered orally QD with food. (revised per Amendment 05)

**Study Treatments (Extension Phase)** (revised per Amendments 07 and 08)

Elenbecestat tablets of 50-mg dose strengths will be supplied during the Extension Phase. Each subject will take 1 tablet orally QD, with or without food.

**Duration of Treatment**

**Core Study**

The maximum duration of a subject's participation in the study will be approximately 2 years, comprising the following:

- Screening and Baseline Periods (Prerandomization Phase): up to 60 days, plus an additional window of up to 30 days if required (revised per Amendment 02)

  (In subjects who have an active infection within 4 weeks of the planned randomization date, the duration of the pre-randomization phase can be extended by up to 4 weeks to allow additional time for resolution of the infection.)
- Treatment Period (Randomization Phase): up to 78 weeks
- Follow-up Period (Randomization Phase): 12 weeks (post last dose)

**Extension Phase** (revised per Amendments 07 and 08)

The duration of the Extension Phase will be approximately 220 weeks, comprising the following:

- Treatment Period: up to 208 weeks (48 months)
- Follow-up Period: 12 weeks (after the last dose)

**Concomitant Drug/Therapy (Core Study and Extension Phase)** (revised per Amendments 04 and 07)

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit in the Core Study (for subjects participating in the Core Study only) or the last treatment visit in the Extension Phase (for subjects participating in the Extension Phase) (see Appendix 2 for a detailed listing of these agents) (revised per Amendment 07):

- Drugs that may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization.
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization.
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines.
- Ig therapy and biologic drugs are not permitted within 6 months before randomization.
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization. However, during the Treatment Period of the study, short term (not more than 14 days) use of steroids up to the equivalent of prednisolone 40 mg QD is permitted after discussion with the medical monitor. Dosing with study drug should be suspended from the time steroid treatment is started. Complete blood count and lymphocyte subsets (for Core Study and first 12 months of Extension Phase only) should be determined before starting steroid treatment and continue to be monitored weekly. (revised per Amendment 08) Study drug may be resumed after discussion with the medical monitor when the following conditions are met: (1) treatment with steroids has been completed for at least 1 week; (2) absolute lymphocytes not <LLN; (3) no lymphocyte subsets are below the discontinuation threshold (for Core Study only); (4) the investigator considers that

the medical condition which required treatment with steroids has improved or resolved. Weekly testing of lymphocyte subset counts (for Core Study only) and CBC with differentials (for Core Study and Extension Phase) is required for 4 weeks following resumption of study drug administration. (revised per Amendment 04)

- (revised per Amendments 06 and 08)

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for any efficacy analyses. (revised per Amendment 05)

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed. Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before randomization. They may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 04)
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if, in the opinion of the investigator, this will not interfere with study procedures or subject safety, and are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks

Antiplatelet therapy: (revised per Amendment 04)

- For subjects who consent to CSF sample collection: Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) are permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.
- For subjects who do not consent to CSF sample collection: Aspirin and clopidogrel, individually or in combination, are permitted.

**Assessments**

**Efficacy Assessments (Core Study)**

Alzheimer's Disease Assessment Scale - cognitive subscale: The 14-item version will be used since it is considered more relevant for subjects with MCI/Prodromal AD or mild AD.

Clinical Dementia Rating: Assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

Mini-Mental State Examination: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing.

International Shopping List Task: The ISLT is a verbal learning and episodic memory test assessing

both immediate and delayed recall.

CogState Brief Battery: A computer-based battery comprising 4 cognitive tests:

- Detection – a simple reaction time test. Speed of response is the measure.
- Identification – a simple choice reaction time test. Speed of response is the measure.
- One Card Back – a simple working memory test. Accuracy of response is the measure.
- One Card Learning – a visual learning and memory test. Accuracy of response is the measure.

Functional Assessment Questionnaire: The FAQ has 10 items concerned with performing daily tasks necessary for independent living. The caregiver or informant provides performance ratings on 10 complex activities of daily living performed within the preceding 4 weeks. (revised per Amendment 04)

Volumetric Magnetic Resonance Imaging: vMRI will be used to evaluate disease modification, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs.

**Pharmacokinetic Assessments (Core Study)**

Blood samples will be collected for the determination of the concentrations of elenbecestat. For subjects who consent to CSF sample collection, CSF samples will be collected for the determination of elenbecestat concentrations. (revised per Amendment 02) Analyses of metabolite concentrations may be performed depending on emerging data from other studies with elenbecestat.

**Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments (Core Study)**

Brain atrophy will be measured by vMRI: see Efficacy Assessments (above).

The soluble biomarkers Aβ(1-x), Aβ(1-42), (Aβ(1-40), total tau (t-tau), and p-tau will be measured in subjects who consent to CSF sample collection (revised per Amendment 02). BACE1 levels and activity in CSF may also be measured in subjects who consent to CSF sample collection (revised per Amendment 02). Other exploratory biomarkers and amyloid isoforms (eg, Aβ[1-40]) may also be evaluated in plasma or CSF. (revised per Amendment 04) Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

Amyloid PET imaging will be used to confirm that all subjects eligible for progression to the Baseline Period have amyloid deposition in the brain. An historical amyloid positive PET scan may be used, if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02) Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses. (revised per Amendments 02 and 05)

Apolipoprotein E (*ApoE*) and N-acetyltransferase 2 (*NAT2)* genotyping/phenotyping will be conducted. *ApoE4* homozygous or heterozygous status versus non-carriers and *NAT2* status will be used in the statistical analysis to determine the effects on treatment response and safety. Remaining genomic DNA may also be stored for up to 15 years to be used to examine the role of DNA sequence variability on the absorption, distribution, metabolism, and elimination of elenbecestat, development of adverse events (AEs), as well as the underlying AD. Variations in elenbecestat exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of

single-nucleotide polymorphisms with PK, safety, or PD data.

**Safety Assessments (Core Study)**

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR. (revised per Amendment 01) Routine safety assessments will include the monitoring and recording all AEs and serious adverse events (SAEs), monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

Complete blood counts and lymphocyte subset absolute counts and percentages will be measured (by a centralized laboratory) every week for the 1st month, every 2 weeks for the next 2 months (Months 2 and 3) and monthly for the next 3 months (Months 4, 5, and 6). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at all 4 Follow-Up Visits at 2, 4, 8, and 12 weeks after the last dose of study drug. Serum IgG, IgA, and IgM will be monitored monthly for the 1st 3 months, at 6, 12, and 18 months, and at the Follow-Up Visits that occur 4, 8, and 12 weeks after the last dose of study drug. (revised per Amendment 04)

Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and posttreatment for exploratory immunomodulatory and immune-based analyses.

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at baseline and at 3-month intervals during the Treatment Period. These assessments will specifically include evaluation of any areas of depigmentation or rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregivers or informants will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so such AEs can be reviewed promptly.

Baseline and on-study blood and DNA samples will be taken and stored for all subjects, and CSF samples will be taken and stored for all subjects from whom CSF samples were collected (revised per Amendments 02 and 04). These samples may be tested for exploratory biomarkers associated with study drug or disease, or in the event that a subject develops AEs that warrant further investigation (eg, to test if a subject with a treatment-emergent infection was exposed to any suspected infective agents before treatment with study drug).

Safety brain MRI assessments will be performed at Screening, at 6, 12, and 18 months during the Treatment Period and at the final Follow-up Visit. Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Full neurologic examinations will be performed at Baseline, at 6, 12, and 18 months, and at the 4- and 12-week Follow-up Visits, by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. The neurologic examinations will include muscle strength testing and assessment of cranial nerves including olfaction, with the use of the Brief Smell Identification Test, as well as other parts of the CNS. (revised per Amendment 04)

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments will include the ADAS-cog14, MMSE, and CBB.

An assessment of suicidality using the C-SSRS will be performed at Screening and Baseline and at

regular intervals throughout the Treatment and Follow-up Periods.

An ophthalmic examination (including retinal examination) will be conducted at Baseline. An additional examination will be conducted if the subject experiences visual disturbances during the course of the study.

A number of safety-related criteria for discontinuation of study drug are specified for the study.

**Efficacy Assessments (Extension Phase)** (revised per Amendment 07)

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing.

FAQ: The FAQ has 10 items concerned with performing daily tasks necessary for independent living. The caregiver or informant provides performance ratings on 10 complex activities of daily living performed within the preceding 4 weeks.

vMRI: vMRI will be used to evaluate disease modification, including the changes from the Core Study Baseline and the Extension Phase Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs.

**Pharmacodynamic and Other Biomarker Assessments (Extension Phase)** (revised per Amendment 07)

Exploratory biomarkers and amyloid isoforms (eg, Aβ[1-40]) will be evaluated in plasma.

**Safety Assessments (Extension Phase)** (revised per Amendments 07 and 08)

All subjects will be assessed for their eligibility for the Extension Phase at Visit 21. Where applicable, results of the safety assessments (including laboratory assessment, physical examination, and neurologic examination) conducted during Visit 20 will serve as Visit 21 values for the Extension Phase with the following exceptions: if Visit 21 occurs more than 10 days after Visit 20, all laboratory safety assessments and vital signs must be repeated.

Routine safety assessments will include the monitoring and recording all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, and physical, dermatologic and neurologic examinations at regular intervals.

There will be no centralized dermatological assessments in the Extension Phase. Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregivers or informants will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly.

Full neurologic examinations will be performed at the start of the Extension Phase (Visit 20 or 21) and at every 6 months during the first 24 months of the Extension Phase Treatment Period and every 12 months thereafter. An additional neurologic examination will also be performed at the final Follow-up Visit. The neurologic examinations will include muscle strength testing and assessment of cranial nerves including olfaction, with the use of the Brief Smell Identification Test, as well as other parts of the CNS.

Complete blood counts and percentages will be measured (by a centralized laboratory) every scheduled visit. Lymphocyte subset absolute counts and percentages will also be measured during the first 12 months of the Extension Phase (by a central laboratory) and the results will be reviewed by the sponsor and the members of the DSMB only.

PBMCs will be collected at Extension Phase Baseline (Visit 21), 6 months (Visit 26), 12 months (Visit 28), and 24 months (Visit 32) for exploratory immunomodulatory and immune-based analyses. Blood samples will be collected and stored; these samples may be used for further exploratory biomarker analyses, and/or, in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

Safety brain MRI and vMRI assessments will be performed at Month 24 and Month 48 of the Extension Phase Treatment Period (Visits 32 and 38, or ED Visit). Subjects who discontinue early from the Extension Phase will have safety brain MRI and vMRI assessments at the ED Visit if these assessments have not already been performed during the preceding 90 days. Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Assessment of suicidality using the C-SSRS, will be performed at the start of the Extension Phase (Visit 21) and at Month 24 (Visit 32) and Month 48 (Visit 38) of the Extension Phase Treatment Period. Subjects who discontinue early from the Extension Phase will have assessments of suicidality using C-SSRS at the ED Visit. Clinical assessment of suicidality, collected from both the subject and the caregiver or informant, will be performed at every scheduled interim safety visit that do not include administration of the C-SSRS. At these visits, a positive suicidality assessment (ie, a "yes" response on the clinical assessment of suicidal thinking and behavior) from the subject or the caregiver/informant on the clinical assessment of suicidality will trigger the C-SSRS to be administered. (revised per amendment 08)

**Bioanalytical Methods**

Plasma and CSF elenbecestat concentrations will be measured by a validated liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) in both CSF and plasma will be measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendment 04)

BACE1 levels and activity may be measured using a customized assay. Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

**Statistical Methods**

All statistical tests will be based on the 5% (2-sided) level of significance. (revised per Amendment 05)

**Study Endpoints (Core Study)**

**Primary Endpoint**

- Safety and tolerability, which include incidence of treatment-emergent adverse events (TEAEs) and SAEs, laboratory parameters, vital signs, and ECG parameters (revised per Amendment 05)

**Secondary Endpoints**

(revised per Amendments 02 and 05)

- % reduction of Aβ(1-x) and Aβ(1-42) in CSF relative to baseline after at least 4 weeks and 18 months of treatment

- The population PK parameters of elenbecestat in CSF and plasma, including the effect of intrinsic and extrinsic factors (including NAT2 phenotype)

**Exploratory Endpoints**

(revised per Amendments 01, 02, 04, and 05)

Change from baseline in:

- CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months of treatment
- CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- CSF amyloid and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment (revised per Amendment 06)
- Total hippocampal volume at 12 and 18 months of treatment as measured by vMRI
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months as measured by vMRI
- Amyloid PET standardized uptake value ratio (SUVR) composite at 18 months for brain amyloid levels
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog14, CDR, MMSE, ISLT, CBB, and FAQ

**Study Endpoints (Extension Phase)** (revised per Amendments 07 and 08)

**Primary Endpoint**

- Safety endpoints: AE, vital sign, ECG, physical examination, clinical laboratory test, any relevant test of cognitive function to evaluate decline, and MRI parameters (microhemorrhage, vasogenic edema, and other clinically significant abnormalities).

**Secondary Endpoints**

Changes from Core Study and Extension Phase baselines in:

- MMSE and FAQ at each visit assessed in the Extension Phase
- Plasma amyloid measurements at 12, 24, 36, and 48 months of Extension Phase treatment
- vMRI parameters including, but not limited to, total hippocampal volume, left and right hippocampal volume, whole brain volume, and total ventricular volume at 24 and 48 months of Extension Phase treatment

**Analysis Sets (Core Study)**

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose exploratory efficacy measurement. (revised per Amendment 05)
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least

1 posttreatment PD measurement.

**Analysis Sets (Extension Phase)** (revised per Amendment 07)

- The Extension Phase Safety Analysis Set (OLE-SAS) is the group of subjects who receive at least 1 dose of study drug during the Extension Phase and who had any on-therapy safety data during the Extension Phase. (revised per Amendment 08).
- The Extension Phase Full Analysis Set (OLE-FAS) is the group of subjects who receive at least 1 dose of study drug during the Extension Phase and have at least 1 postdose efficacy assessment during the Extension Phase.
- The Extension Phase PD Analysis Set (OLE-PD) is the group of subjects who have at least 1 posttreatment PD measurement during the Extension Phase.

**Efficacy and Biomarker Analyses** (revised per Amendment 05)

**Analysis for the Primary Endpoint (Core Study)**

There is no primary efficacy endpoint. (revised per Amendment 05)

**Analysis for the Secondary Endpoints (Core Study)**

An mixed-effects model with repeated measures (MMRM) will be used to analyze the following secondary endpoint:

Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) from 4 weeks and up to 18 months. Data from early discontinuations will also be included. (revised per Amendment 05)

**Analysis for Exploratory Endpoints (Core Study)**

(revised per Amendments 01, 02, 04, and 05)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months of treatment
- Change from baseline in CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Change from baseline in plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- Change from baseline in CSF amyloid and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment (revised per Amendment 06)
- Change from baseline in total hippocampal atrophy at 12 and 18 months as measured by vMRI
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months as measured by vMRI
- Change from baseline in Amyloid PET SUVR composite at 18 months for brain amyloid levels

The following efficacy endpoints will be summarized using descriptive statistics:

- Change from baseline in the clinical assessments: ADAS-cog14, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months

The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

**Pharmacokinetic Analyses (Core Study)**

The PK Analysis Set will be used for elenbecestat concentration listings and for summaries of elenbecestat concentrations in plasma and CSF by dose and day. Elenbecestat metabolite PK data may also be listed and summarized. (revised per Amendment 05)

A population PK approach will be used to characterize the plasma PK of elenbecestat. For this approach, plasma PK data from this study will be pooled with relevant data from Phase 1 studies. As appropriate, the effect of covariates on the PK of elenbecestat will be evaluated. The PK model will be parameterized for oral clearance (CL/F) and apparent volume of distribution (Vz/F) for elenbecestat. Derived exposure parameters such as steady state area under the concentration time curve ($AUC_{ss}$) and average concentration ($C_{avg}$) of elenbecestat and other derived parameters will be calculated from the model using the individual estimates parameterized for oral clearance and dosing history. (revised per Amendment 04)

**Pharmacodynamic Analyses (Core Study)**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). The percentage change from baseline in CSF Aβ(1-x), Aβ(1-40), Aβ(1-42), t-tau, p-tau, and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months will be analyzed and presented graphically. (revised per Amendments 04 and 05) Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status. Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses (Core Study)**

The PK/PD relationship between CSF biomarker levels, amyloid load on PET, vMRI, and elenbecestat dose, plasma and CSF exposure will be initially explored graphically and any emergent relationship will be explored through population PK/PD modeling. Additionally, the relationship between CSF exposure to elenbecestat and the change from baseline for 18 months in the ADAS-cog, the CDR, and the MMSE will be explored graphically. (revised per Amendments 04 and 05)

Additionally, the relationship between plasma exposures of elenbecestat and select lymphocyte parameters will be explored graphically, and any emergent relationship will be explored using population-based modeling methods. (revised per Amendment 04)

**Pharmacogenomic Analyses (Core Study)**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. Further information is in the "Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments" section. Details of pharmacogenomic testing may be provided and reported separately.

**Safety Analyses (Core Study)**

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements, and cognitive decline assessment such as CBB will be summarized by treatment group using descriptive statistics. (revised per Amendment 05)

Lymphocyte Subsets

Lymphocyte subsets, including but not limited to, CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cells), CD16/CD56 (natural killer cells), and CD14 (macrophages) and regulatory T cells will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose.

Serum IgG, IgM, IgA will be measured and summarized in the same manner as other laboratory parameters. (revised per Amendment 04)

**Interim Analyses Core Study**

In order to make decisions about the remainder of the study as well as the full elenbecestat clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. Investigators, other clinical site staff, subjects, caregivers/informants and study team will remain blinded to study treatment. (revised per Amendments 03 and 05)

An interim safety analysis will also be conducted when 60 subjects (±20%) have completed 12 weeks of treatment (or discontinue study drug early). (revised per Amendments 01, 03, 04, and 05)

**Stratification Core Study**

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

**Efficacy Analyses (Extension Phase)** (revised per Amendments 07 and 08)

The following secondary efficacy endpoints will be summarized by descriptive statistics and/or graphs, using OLE-FAS:

- Changes from Core Study and Extension Phase baselines in MMSE and FAQ scores
- Changes from Core Study and Extension Phase baselines in vMRI parameters including, but not limited to, total hippocampal volume, left and right hippocampal volume, whole brain volume, and total ventricular volume at 24 and 48 months

The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

**Pharmacodynamic Analyses (Extension Phase)** (revised per Amendments 07 and 08)

The OLE PD Analysis Set will be used for the summaries and analyses of PD biomarkers. The percentage change in plasma amyloid measurements from Core Study and Extension Phase baselines to 12, 24, 36, and 48 months of Extension Phase treatment will be analyzed and presented graphically.

**Safety Analyses (Extension Phase)** (revised per Amendment 07)

Safety analysis will be performed similarly to the Core Study. Evaluations of safety will be performed on the OLE-SAS. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS and clinical assessment of suicidality), and changes from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements, and cognitive decline assessment such as MMSE will be summarized by using descriptive statistics.

**Sample Size Rationale**

A total of 15 subjects per dose is deemed sufficient to derive adequate safety and PK/PD data to aid in the selection of appropriate doses and the design of the Phase 3 studies that may be planned subsequently. (revised per Amendment 04) Based upon the selection of the elenbecestat 50-mg dose for the Phase 3 studies, subjects randomized to the active treatment arms will be re-assigned to the selected 50-mg dose for further evaluation. (revised per Amendment 06)

# 3 TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES



## LIST OF IN-TEXT FIGURES



## LIST OF APPENDICES

# 4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| Aβ | amyloid β |
| Aβ(1-x) | amyloid β (1-x) (ie, the amyloid β monomer from amino acid 1 to x [eg, 1-42]) |
| AChEI | Acetylcholinesterase inhibitor |
| AD | Alzheimer's disease |
| ADAS-cog | Alzheimer's Disease Assessment Scale - cognitive subscale |
| AE | adverse event |
| ApoE | apolipoprotein E |
| $AUC_{(0\text{-}24h)ss}$ | area under the concentration × time curve at steady state from time zero to 24 hours |
| $AUC_{ss}$ | steady state area under the concentration × time curve |
| BACE1 | Beta (β)-amyloid converting enzyme 1 |
| BP | blood pressure |
| bpm | beats per minute |
| $C_{avg}$ | average concentration |
| CBB | CogState Brief Battery |
| CBC | complete blood count |
| CBP | childbearing potential |
| CDR | Clinical Dementia Rating |
| CES2 | carboxyesterase-2 |
| CFR | Code of Federal Regulations |
| CL/F | oral clearance |
| $C_{max,ss}$ | maximum plasma concentration at steady state |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| CRA | clinical research associate |
| CRF | case report form |
| CRO | contract research organization |
| CSF | cerebrospinal fluid |
| $C_{ss,av}$ | average steady-state concentration |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CTA | Clinical Trial Agreement |
| CYP | cytochrome P450 |
| DSMB | data safety monitoring board |
| eCRF | electronic case report form |

| Abbreviation | Term |
|---|---|
| ED | early discontinuation |
| ELISA | enzyme-linked immunosorbent assay |
| FAQ | Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire) |
| FAS | Full Analysis Set |
| FLAIR | fluid-attenuated inversion recovery |
| GCP | Good Clinical Practice |
| GDS | Geriatric Depression Scale |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |
| HCVAb | hepatitis C virus antibody |
| HSV | herpes simplex virus |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ID | identifier |
| IEC | Independent Ethics Committee |
| Ig | immunoglobulin (eg, IgA, IgG, IgM) |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISLT | International Shopping List Task |
| IxRS | interactive voice and web response system |
| LLN | lower limit of normal |
| LNH | low/normal/high |
| LP | lumbar puncture |
| MAD | multiple ascending dose |
| MCI | mild cognitive impairment |
| MCI/Prodromal | mild cognitive impairment due to Alzheimer's disease/ prodromal Alzheimer's disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mild to moderate AD | mild to moderate dementia due to Alzheimer's disease |
| miRNA | micro-ribonucleic acid |
| MMRM | mixed-effects model with repeated measures |
| MMSE | Mini-Mental State Examination |
| MRI | magnetic resonance imaging |
| NAT2 | N-acetyltransferase 2 |

| Abbreviation | Term |
|---|---|
| NIA-AA | National Institute on Aging-Alzheimer's Association |
| OLE | Open-label Extension |
| OLE-SAS | Extension Phase Safety Analysis Set |
| PBMC | peripheral blood mononuclear cell |
| PD | pharmacodynamic(s) |
| PET | positron emission tomography |
| PGx | pharmacogenomic(s) |
| PK | pharmacokinetic(s) |
| PRN | Pro re nata |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| p-tau | phosphorylated-tau |
| QD | once daily |
| QTc | corrected QT interval |
| QTcF | QTc interval calculated using Fridericia's formula |
| R | randomization |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reaction |
| SUVR | standardized uptake value ratio |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |
| TEMAV | treatment-emergent markedly abnormal laboratory values |
| t-tau | total tau |
| ULN | upper limit of normal |
| UNS | unscheduled |
| vMRI | volumetric magnetic resonance imaging |
| Vz/F | apparent volume of distribution |
| WHO DD | World Health Organization Drug Dictionary |
| β-hCG | beta-human chorionic gonadotropin |

# 5 ETHICS

## 5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 GCP), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA][s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigators or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

## 5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (CFR) (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

- European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved European Union member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

## 5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject and the identified caregiver or informant, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or understand it or if the identified caregiver or informant is unable to read, an impartial witness should be present during the entire informed consent discussion. If, in the investigator's opinion, a subject lacks capacity to consent, the subject's assent should be obtained in addition to the written informed consent of a legal representative (capacity to consent and definition of legal representative should be determined in accordance with applicable local laws and regulations). (revised per Amendment 01) After the ICF and any other written information to be provided to subjects is read and explained to the subject and the identified caregiver or informant, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified caregiver or informant should also consent to supporting the subject's participation in the study and will be provided with a separate written ICF for his or her participation in the study, to be signed before he or she participates in any further aspects of the study.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified caregiver or informant must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified caregiver or informant will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified caregiver or informant should be

informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

All subjects will also be asked to provide written consent for cerebrospinal fluid (CSF) sampling at Baseline and after receiving study drug for from 4 weeks and up to 18 months (or at Early Discontinuation [ED]) during the Core Study. This consent for CSF sample collection is not required for study eligibility. (revised per Amendments 02 and 05)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects and will be via a separate, optional CSF consent form for the study. (revised per Amendment 04)

# 6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 35 investigational sites in the United States. (revised per Amendments 01, 02, 04, and 05)

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

# 7 INTRODUCTION

At this time, there is no cure for Alzheimer's disease (AD), no known way of slowing down the progression of this disease, and no approved treatment available to reverse the deterioration. There is, therefore, an urgent unmet medical need for drugs that slow or prevent disease progression. Beta-amyloid converting enzyme 1 (BACE1) is a key enzyme responsible for the production of amyloid β (Aβ) peptides and plaque formation, and several reports have described elevated levels of BACE1 in AD brains (Coulson, et al., 2010; Lu, et al., 2012). Once amyloid plaques form, Aβ causes BACE1 levels to increase further, thus accelerating Aβ generation and plaque growth via a positive feedback loop. Therefore, BACE1 is a promising target for modifying or treating AD.

It is now widely accepted that mild cognitive impairment (MCI) due to AD and mild to moderate AD dementia are stages on a single disease spectrum, which follows an Alzheimer's pathological cascade. (revised per Amendment 01) Recent consensus papers from the international workgroups of the National Institute on Aging-Alzheimer's Association (NIA-AA), have endorsed this hypothesis (Albert, et al., 2011; Jack, et al., 2011; McKhann, et al., 2011; Rosen, et al., 1984; Sperling, et al., 2011).

From a clinical standpoint, demonstration of an effect on slowing disease course is hampered by the lack of sensitive tools for detecting relatively small changes in progression or treatment effect especially in early disease. In addition, drugs that are expected to slow disease progression require longer study durations to ensure adequate separation from placebo. These challenges have resulted in the use of biomarkers as surrogates for clinical effect in Phase 2 studies, in order to facilitate the development process for disease modifying agents. However, subsequent Phase 3 AD studies based solely on biomarker findings in Phase 2 have failed to show clinical effect, due, in part, to the fact that biomarkers may not predict clinical outcomes for potential disease modifying agents. These findings underscore the need for innovative approaches to clinical study design for measuring the effect of treatment.

Elenbecestat (E2609) is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, elenbecestat inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in cerebrospinal fluid (CSF) and plasma (rat, guinea pig, and monkey). In humans, elenbecestat has been shown to inhibit BACE1 enzyme activity in CSF and lower the levels of Aβ, including amyloid beta monomer from amino acid 1 to x (Aβ[1-x]), Aβ(1-40) and Aβ(1-42), in CSF both in vitro and in vivo. See the Investigator's Brochure for additional information. The target indication for elenbecestat is therefore treatment and disease modification of AD.

The present clinical study is a Phase 2 study for the elenbecestat program, and is designed to establish safety in subjects with MCI due to AD/Prodromal AD (referred to as MCI/Prodromal throughout the protocol) and in subjects with mild to moderate AD. (revised per Amendment 05) This study will include a Core Study of approximately 32 months (including the Prerandomization and Randomization Phases) and an Open-label Extension Phase of up to 51 months. (revised per Amendments 07 and 08) Results from the Core Study

will guide both the decision to move into Phase 3 development and the selection of the dose strengths to be taken into Phase 3.

In the MCI/Prodromal and mild to moderate AD population, the Core Study will compare placebo and 3 oral doses of elenbecestat (5, 15, and 50 mg) administered once daily (QD) for 18 months. (revised per Amendment 05)

The Core Study will include interim evaluations of the pharmacokinetic (PK), pharmacodynamic (PD), safety, and tolerability of chronic dosing with elenbecestat. (revised per Amendment 05) Furthermore, there will be close monitoring of safety by an independent data safety monitoring board (DSMB), including a formal safety review as soon as the randomized subjects (n=60, ±20%) have completed at least 12 weeks of treatment, have discontinued study drug or have withdrawn from the study. (revised per Amendments 04 and 05) The study also includes a number of exclusion criteria, specific blinded safety monitoring procedures and safety criteria for discontinuation of study drug in light of the preclinical and clinical safety data collected to date following administration of elenbecestat.

The Extension Phase will evaluate the long-term safety and tolerability of elenbecestat; a detailed description of the Extension Phase is provided in Appendix 6. (revised per Amendment 07)

## 7.1 Results of Interim Evaluations

(revised per Amendment 06)

Unblinded interim evaluations of the safety and tolerability of elenbecestat suggested favorable safety at all doses of elenbecestat. Additionally, analyses of the PD effects (reduction from baseline in CSF Aβ levels) of elenbecestat 5, 15, and 50 mg per day have indicated that elenbecestat 50 mg per day produced relatively high levels of CSF Aβ reduction (greater than 50%). Based on the results of these analyses, elenbecestat 50 mg per day has been selected as the dose for Phase 3 development.

As elenbecestat 5 and 15 mg per day will not be advanced clinically, subjects initially randomized to the elenbecestat 5 and 15 mg per day treatment arms will be re-assigned in a blinded manner to the elenbecestat 50 mg treatment arm provided that they will have at least 12 weeks of treatment remaining in the Randomization Phase. The purpose of this dose re-assignment is to further characterize the safety and tolerability of elenbecestat 50 mg.

## 7.2 Nonclinical and Clinical Safety Data

The toxicity of elenbecestat has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by elenbecestat in a

clinical setting. Further details of the nonclinical data to date with elenbecestat can be found in the Investigator's Brochure.

The clinical program to date includes 6 Phase 1 studies:

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, single ascending dose (SAD) study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50-mg dose only, aged 65 to 85 years).

Study E2609-A001-002 (Study 002) was a randomized, double-blind and placebo-controlled, multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of elenbecestat (E2609) and the PD effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of elenbecestat. It also investigated the effects of elenbecestat on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-005 (Study 005) was an open label, single-dose study to determine the metabolism and elimination of [$^{14}$C]-elenbecestat (E2609) in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of elenbecestat under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) was a randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with elenbecestat. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with elenbecestat. In elderly subjects treated with 50 mg of elenbecestat, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or ECG parameters. The 800 mg (maximum) dose was associated with a small increase of QTc interval calculated using Fridericia's formula (QTcF) from baseline (14.9 msec at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose

of elenbecestat might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that elenbecestat altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of elenbecestat. A single dose of elenbecestat up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, elenbecestat administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of elenbecestat on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP]3A4 and carboxyesterase-2 [CES2]) increased by approximately 70% the AUC of elenbecestat. Consequently, strong inhibitors of CYP3A4 will be prohibited in this study.

Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of elenbecestat. Therefore, no restrictions are required for the use of concomitant medications which are known to be inducers of CYP450 enzymes. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of elenbecestat when coadministered with elenbecestat but not when dosed at least 2 hours apart from elenbecestat. Elenbecestat (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of elenbecestat. Therefore, on the basis of drug interaction considerations, the only restriction of concomitant medications is that for strong inhibitors of CYP3A4.

# 8 STUDY OBJECTIVES

Objectives for the Extension Phase are provided in Appendix 6. (revised per Amendment 07)

## 8.1 Primary Objective

(revised per Amendment 05)

The primary objective is:

- To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with elenbecestat in MCI/Prodromal subjects and in subjects with mild to moderate AD (revised per Amendment 01)

## 8.2 Secondary Objectives

The secondary objectives are: (revised per Amendments 02 and 05)

- To characterize the plasma and CSF PK of elenbecestat
- To assess the effects of elenbecestat on Aβ(1-x) and Aβ(1-42) in CSF from 4 weeks and at 18 months of treatment

## 8.3 Exploratory Objectives

(revised per Amendments 01, 02, 04, and 05)

The exploratory objectives are:

- To explore the effects of elenbecestat compared on CSF Aβ(1-40) and BACE1 measurements from 4 weeks and up to 18 months of treatment
- To explore the effects of elenbecestat compared with placebo on various biomarkers. Biomarkers to be explored may include, but not limited to:
  a. CSF biomarkers of neurodegeneration (eg, total tau [t-tau], phosphorylated-tau [p-tau]) after 18 months of treatment
  b. Plasma and CSF amyloid, and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment (revised per Amendment 06)
  c. Total hippocampal atrophy at 12 and 18 months of treatment, as measured by volumetric magnetic resonance imaging (vMRI)
  d. vMRI measurements including left and right hippocampal volume, whole brain volume, and total ventricular volume at 6, 12, and 18 months of treatment
  e. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)

- To explore the effects of elenbecestat compared with placebo on clinical status at various time points during 18 months of treatment, and during posttreatment follow-up by assessment of:
  a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog14)
  b. The Clinical Dementia Rating (CDR) scale
  c. The Mini-Mental State Examination (MMSE)
  d. The International Shopping List Task (ISLT)
  e. The CogState Brief Battery (CBB)
  f. The Functional Assessment Questionnaire (FAQ; (also known as the Functional Activities Questionnaire)
- To explore the relationship between the treatment effects of elenbecestat on measured clinical efficacy scales (eg, MMSE, CDR) and its effects on CSF amyloid, CSF amyloid isoforms, brain amyloid, and vMRI
- To explore relationships between both elenbecestat dose and exposure, with PD and safety endpoints

# 9 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan

This study is a multicenter, placebo-controlled, double-blind, parallel-group, randomized, dose-finding study with an Extension Phase of up to 51 months in subjects with MCI/Prodromal AD or mild to moderate AD. (revised per Amendments 01, 07, and 08)

A common set of inclusion criteria, consistent with the NIA-AA clinical research criteria for MCI due to AD or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study consists of 3 phases: Prerandomization, Randomization, and Extension Phase. The Prerandomization and Randomization Phases are referred to as the Core Study throughout the protocol. (revised per Amendment 07).

The Prerandomization Phase (up to 60 days, plus an additional window of up to 30 days if required [revised per Amendment 02]) will consist of a Screening Visit and a Baseline Visit. Screening assessments will be organized into 4 tiers; see Section 9.5.2.2, Table 6, and Figure 2.

All screening assessments must be completed, and eligibility to continue to the Baseline Period confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-up (post last dose; 12 weeks).

All subjects (MCI/Prodromal and mild to moderate AD) will initially be randomized 1:1:1:1 to 4 treatment groups (5, 15, or 50 mg elenbecestat or placebo) (revised per Amendments 01 and 05). Upon implementation of Amendment 06, at the next regularly scheduled visit, subjects receiving elenbecestat 5 or 15 mg who have not yet completed Visit 17 (Week 66), will be re-assigned in a blinded manner to elenbecestat 50 mg for the remainder of the Treatment Period. In order to maintain the blind, all subjects who have not yet had Visit 17 will go through the same procedures with the placebo-randomized subjects continuing to receive placebo and those randomized to elenbecestat 50 mg continuing to receive 50 mg. (revised per Amendment 06)

All subjects who complete 18 months of treatment and 12 weeks of follow-up in the Core Study and who satisfy the entry criteria for the Extension Phase are eligible to enter the Extension Phase. During the Extension Phase, subjects will receive elenbecestat 50 mg daily for up to 48 months (4 years). (revised per Amendment 08)

An overview of the Core Study design is presented in Figure 1.

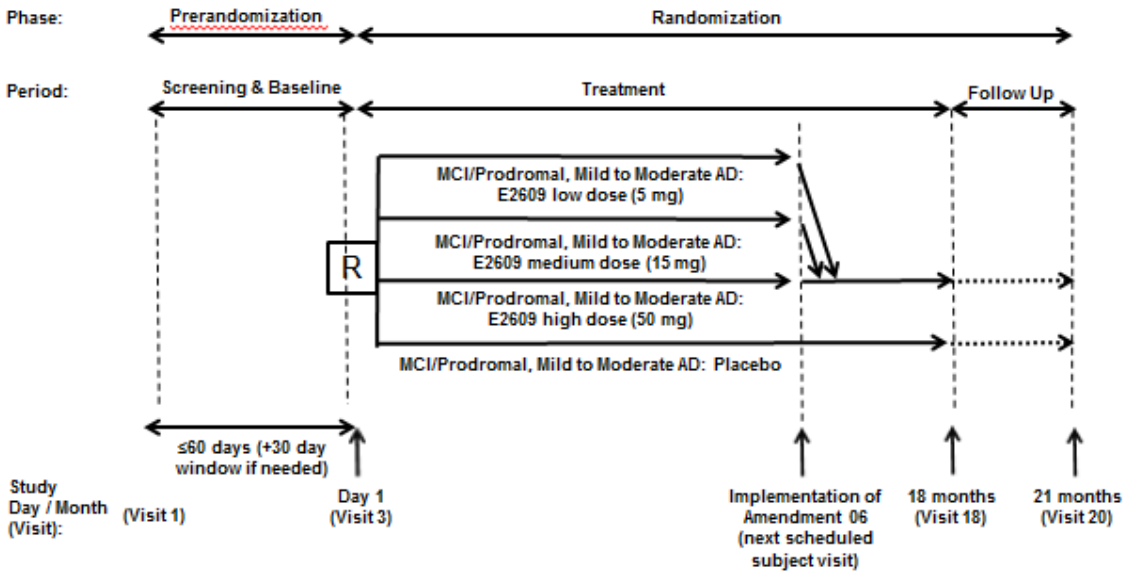


**Figure 1 Design of Core Study E2609-G000-202**

(revised per Amendments 01, 02, 05, and 06)

R = randomization, AD = Alzheimer's disease, MCI = mild cognitive impairment

This study will be limited to approximately 35 sites in the United States, with approximately 60 (±20%) eligible subjects randomized at Visit 3, 1:1:1:1 to 4 treatment groups within each clinical cohort. In addition to the placebo group, 3 doses of elenbecestat will be used to reduce CSF Aβ levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/PD modeling shows these doses should achieve these targets when administered QD with food and will be evaluated based on the 4-week (or later) assessment of CSF Aβ(1-x) from subjects who provide voluntary consent for CSF measurement (see Section 9.4.4 ). (revised per Amendments 01, 02, 04, and 05) Safety data will be monitored in a blinded fashion on a regular basis.

In addition, approximately every 3 months from the time the 1st subject is randomized into the study through the time the last subject is randomized, an independent DSMB (including at least 1 immunologist) will review all safety data in an unblinded manner. (revised per amendment 06) The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. (revised per Amendments 01, 04, and 05)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

Interim analyses of the elenbecestat plasma PK for all subjects and the elenbecestat CSF PK and PD profiles will be performed on baseline data and samples collected after at least 4 weeks of treatment in the Core Study. (revised per Amendment 05 and 07) Refer Section 9.7.3 for more detail. These data will be used to evaluate the CSF PD effects of elenbecestat doses, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels (see Section 9.4.4). The median and mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks or more of treatment for each dose of elenbecestat and the 90% CI for the median will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data and will relate the average steady state plasma concentration of elenbecestat to steady state CSF Aβ(1-x) percentage reduction from baseline determined after at least 4 weeks of dosing. (revised per Amendments 01, 02, 03, and 04)

Once subjects have completed at least 12 weeks of treatment in the Core Study (or discontinued study drug early), an interim safety analysis will be conducted by Eisai and the DSMB. (revised per Amendments 01, 04, and 05) At the completion of this interim safety review, the frequency of subsequent unblinded safety reviews will be re-evaluated by the DSMB and the sponsor and this information will be provided in the DSMB charter. (revised per Amendment 06) Subjects will continue study drug while the DSMB reviews all the available safety data. (revised per Amendment 05) At the time of this interim safety analysis, some subjects will have more than 12 weeks of safety data.

Interim analyses are planned and are discussed in Section 9.7.3. (revised per Amendment 03)

Based on the results of the interim analyses, the elenbecestat 50 mg dose has been chosen as the clinical dose for the Phase 3 studies. In order to collect additional safety data for elenbecestat 50 mg, subjects randomized to elenbecestat 5 or 15 mg in this study will be re-assigned to elenbecestat 50 mg if and only if these subjects have at least 12 weeks of treatment remaining in the Randomization Phase following study drug dose re-assignment. Therefore, subjects who completed Visit 17 assessments before the implementation of Amendment 06 will remain on their original randomized dose. As study drug dose re-assignment will occur in a blinded manner, a 4-week interim safety assessment following study drug re-assignment will be required for all subjects. (revised per Amendment 06)

### 9.1.1 Prerandomization Phase

The Prerandomization Phase includes a Screening Visit and a Baseline Visit. All Screening Visit assessments must be completed and eligibility to progress must be confirmed before any Baseline Visit assessments are performed. All Screening Visit and Baseline Visit assessments must be completed within 50 days (plus an additional window of up to 30 days if required [revised per Amendment 02]) and a window of no more than 10 days is to be observed between the completion of all Baseline Visit assessments (including confirmation of eligibility following all Baseline Visit assessments) and randomization into the study at Visit 3 (revised per Amendment 02). Thus, the Prerandomization Phase will last for up to 60 days, plus an additional window of 30 days if required (revised per Amendment 02). The

series of assessments conducted during this phase will determine eligibility for randomization into the study.

Inclusion criteria are discussed in Section 9.1 and detailed in Section 9.3.1. Before randomization, the clinician will provide a judgment on the classification of a subject as either MCI/Prodromal or likely mild to moderate AD. (revised per Amendment 01) This judgment may be discussed and reviewed with the sponsor or sponsor's representative, as necessary.

Results of the Screening safety magnetic resonance imaging (MRI) will be valid for 90 days from the date of scanning. Results of the lumbar puncture (LP) from subjects who voluntarily consent for CSF measurement will be valid for 90 days from the date of testing. Results of Screening PET scans conducted specifically for this study and for use in the longitudinal analyses will also be valid for 90 days from the date of scanning. These assessments will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. Historical PET scans used for determination of eligibility only (ie, not used for the longitudinal analyses) are valid for 12 months. (revised per Amendment 02)

#### 9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and caregiver or informant, and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained from both the subject and the caregiver or informant. The caregiver or informant needs to be present at this visit.

Study site personnel will interview the subject and caregiver or informant to obtain demographic and clinical information as described in Table 6, and will review inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2 and perform any required assessments in order to complete these criteria. Prior medications and medications currently being taken by the subject will be reviewed (see Section 9.4.7). The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

Clinical assessments for eligibility will be conducted during the Screening Visit as described in Table 6 and Figure 2.

Every effort should be made to conduct these assessments in the morning, but if this is not possible, they should be conducted at the same time of day at all subsequent visits. The Screening assessments/procedures have been organized into 4 distinct tiers (Table 6 and Figure 2). All assessments/procedures in each tier should be completed, and eligibility to continue screening in the study confirmed, before any assessments/procedures from the next tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures as

long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. (revised per Amendment 01)

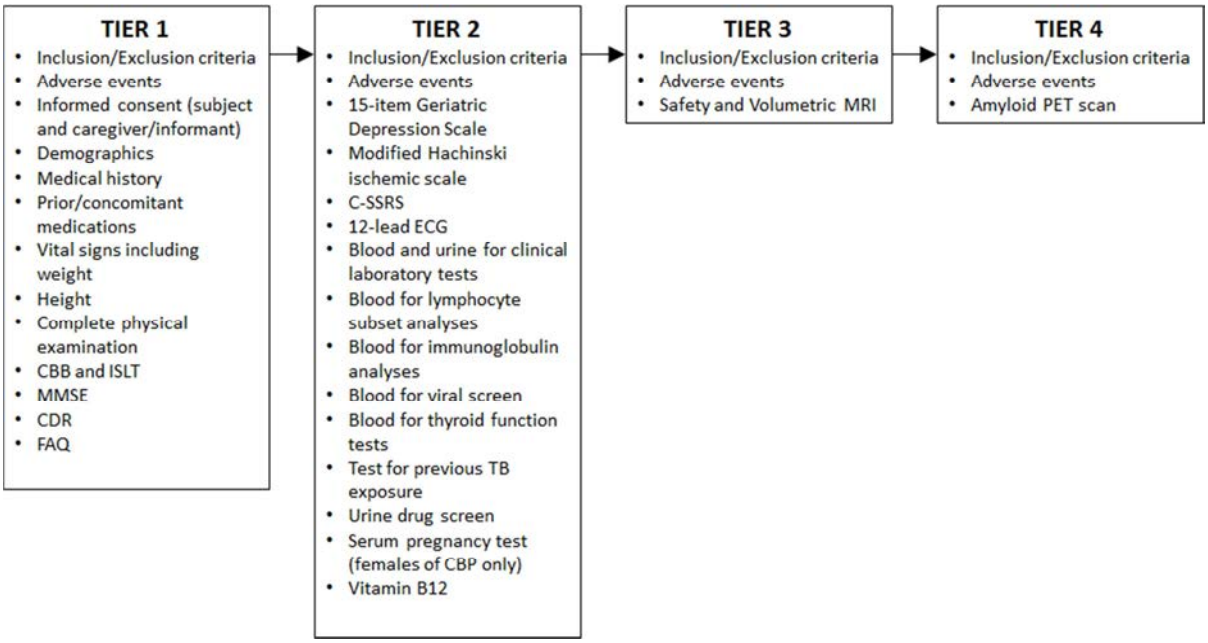


**Figure 2 Assessments to be Performed at Screening by Tier**

CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), ISLT = International Shopping List Task (immediate and delayed recall), MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PET = positron emission tomography, TB = tuberculosis.

Cognitive assessments (Tier 1) are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). The recommended order of assessments at Screening is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. (revised per Amendment 02) The investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session (Tier 3).

Amyloid PET imaging will be used to confirm all subjects have amyloid deposition in the brain (Tier 4). An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. If an historical amyloid positive PET scan is being used, it should be submitted to the central PET reading group after the subject has completed and passed all Tier 1 assessments. (revised per Amendment 02)

#### 9.1.1.2 Baseline Period

All Screening Visit assessments must be completed (and eligibility to progress confirmed) before any Baseline Visit assessments are performed. The Baseline Visit assessments (per Table 6 and Section 9.5.1.2) are to be completed as soon as possible after completion of the final Screening Visit assessment (ie, PET scan) such that all Screening Visit and Baseline Visit assessments are completed within 50 days, plus an additional window of up to 30 days if required. (revised per Amendment 02)

Inclusion and exclusion criteria will again be reviewed, vital signs including weight will be recorded, and a 12-lead ECG will be conducted in triplicate. A routine physical examination will be conducted and a dermatological assessment and neurological examination (including the Brief Smell Identification Test [Sensonics Inc.]) will be performed. (revised per Amendment 04) A urine pregnancy test will be conducted for females of childbearing potential. Blood will be collected from all subjects for clinical chemistry and hematology, lymphocyte subset analyses, Ig analyses, and PD assessments. Blood samples will be collected and stored for determination of a subject's previous exposure to infective pathogens in the event of AEs that warrant further investigation occurring at a later point in the study. Psychometric assessments will be administered to the subject in the order stated in Table 6. The caregiver or informant needs to be present at this visit. The Columbia Suicide Severity Rating Scale (C-SSRS) will also be administered (Section 9.5.1.5.11).

For subjects who consent to CSF sample collection, a CSF sample will be obtained at this visit for PK and PD assessments (see Section 9.5.1.4). (revised per Amendment 02)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

Blood will be collected from all subjects for pharmacogenomic (PGx) analyses of apolipoprotein E (*ApoE*) and the N-acetyltransferase 2 (*NAT2)* phenotype of subjects enrolled in the study (see Section 9.7.1.7.2).

### 9.1.2 Randomization Phase

Subjects who complete the Baseline Visit assessments, and are eligible based on the inclusion and exclusion criteria (see Section 9.3.1 and Section 9.3.2), will begin the Randomization Phase no more than 10 days after completion of the Baseline Visit assessments and confirmation of the eligibility of the subject based on the results of all the Baseline Visit assessments (revised per Amendment 02).

The Randomization Phase will consist of a Treatment Period of 78 weeks duration and a Follow-up Period of 12 weeks after the last dose of study drug.

#### 9.1.2.1 Treatment Period

Subjects will be randomized at the beginning of the Treatment Period and will receive study drug or placebo, to be administered orally QD with food. Double-blinding to study drugs will be in effect throughout the Treatment Period. (revised per Amendment 06)

Safety criteria for discontinuation of study drug are detailed in Section 9.3.3.

Subjects will attend the study site every week for the first 4 weeks after beginning study drug, then fortnightly until 12 weeks have elapsed since first dose. Visits will then be conducted at 16, 20, 26, 39, 52, 65, and 78 weeks after the first dose.

#### 9.1.2.2 Early Discontinuation

Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. Follow-up Visits will also be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug. (revised per Amendments 04 and 05)

#### 9.1.2.3 Follow-Up Period

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 4 posttreatment Follow-up Visits: 2, 4, 8, and 12 weeks after the last dose of study drug. If clinically indicated, more frequent safety assessments can be conducted as part of Unscheduled (UNS) Visits during the posttreatment Follow-up Period. (revised per Amendment 04)

The end of the study will be defined as the date of the clinical database lock (ie, when all study data are collected and data validation is completed).

As required by some regulatory agencies, the following estimates are provided:

- The study will begin in Nov 2014 and is projected to end by Apr 2018. (revised per Amendment 05)
- The maximum estimated period for each subject on study is anticipated to be approximately 2 years.

### 9.1.3 Extension Phase

A complete description of the Extension Phase is provided in Appendix 6; key features are summarized below. (revised per Amendment 07)

After completing all Visit 20 follow-up procedures for the Core Study, eligible subjects will have the option to participate in an open-label Extension Phase within 4 weeks of Core Study Visit 20. These subjects may transition to the Extension Phase immediately following Visit 20 (on the same day) if the decision to proceed with the Extension Phase has been made at that time. The medical monitor must be contacted if Visit 21 (start of the Extension Phase) is to occur more than 4 weeks after Visit 20.

For all subjects, assessments performed at Visit 20 may serve as the Visit 21 (start of the Extension Phase) results with the following exceptions: laboratory assessments and vital signs must be repeated if Visit 21 occurs more than 10 days after Visit 20.

Subjects who are eligible and who consent to participate in the Extension Phase will be administered elenbecestat 50 mg daily at Visit 21. Subjects with pending INR and serum pregnancy test results (female subjects of childbearing potential only) but who are otherwise qualified may begin Extension Phase dosing at Visit 21; however, these subjects must discontinue study drug immediately if either test result meets the exclusion criteria.

During the Extension Phase, safety assessments will continue to be monitored and all AEs and SAEs will be recorded. Vital signs, hematology, blood chemistry, and urine values will

be monitored at every scheduled visit. Clinical assessments (MMSE and FAQ) will be administered every 3 months for the first 24 months and every 4 months thereafter. Blood for PD analyses will be collected after 12, 24, 36, and 48 months of Extension Phase treatment. All subjects will be assessed using safety MRIs and vMRI measurements at 24 and 48 months. Subjects who discontinue early from the Extension Phase will have safety brain MRI and vMRI assessments at the ED Visit if these assessments have not already been performed during the preceding 90 days. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. (revised per Amendment 08)

#### 9.1.3.1 Early Discontinuation

Subjects who prematurely discontinue study drug for any reason will undergo an ED Visit within 7 days of their last dose of study drug. Follow-up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug.

#### 9.1.3.2 Follow-Up

All subjects, regardless of whether they complete all 48 months of treatment in the Extension Phase or prematurely discontinue study drug will complete 2 posttreatment Follow-up Visits at 4 and 12 weeks after the last dose of study drug. If clinically indicated, more frequent safety assessments can be conducted as part of UNS Visits during the Extension Phase Follow-up Period.

## 9.2 Discussion of Study Design, Including Choice of Control Groups

### 9.2.1 Overview

The primary objective of the study is to assess the safety and tolerability of daily dosing with elenbecestat in subjects with MCI/Prodromal AD and in subjects with mild to moderate AD. Immunological and hematological parameters will also be assessed. (revised per Amendment 04)

The inclusion criteria for the MCI/Prodromal cohort will be consistent with the NIA-AA criteria for MCI due to AD (Albert, et al., 2011) and with the definition of Prodromal AD per Dubois et al., 2010 (see Section 9.2.2).

There is no active or positive control for this study as at this time, there is no cure for AD, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

Secondary endpoints include CSF PK and plasma PK parameters of elenbecestat based on population PK analysis and the percentage reduction of Aβ(1-x) and Aβ(1-42) in CSF relative to baseline from 4 weeks and up to 18 months of treatment. The intrinsic and extrinsic factors on the PK characteristics will also be explored.

Exploratory endpoints include CSF Aβ(1-40) and BACE1 measures as well as CSF biomarkers of neuronal degeneration (eg, t-tau and p-tau), volumetric MRI measurements, plasma amyloid measurements, brain amyloid levels as measured by amyloid PET and clinical assessments. (revised per Amendment 05) Exploratory endpoints including assessments of efficacy, safety, and other biomarkers are also included.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups (Section 9.7.4) Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

The rationale for the selection of doses used in the study is provided in Section 9.4.4.

### 9.2.2 Rationale for Study Population

By the time AD progresses to dementia, with loss of functional capabilities, the amyloid load in the brain is approaching a plateau and significant neurodegeneration has occurred (Jack, et al., 2010). Consequently, there is a growing view within the AD field that it may be necessary to initiate disease modifying treatments earlier, before the onset of clinical dementia (Aisen, et al., 2010). However, this hypothesis remains to be demonstrated with clinically effective therapies, and may not apply to all therapeutic classes, it is possible that this consideration explains the failure of the humanized monoclonal antibody bapineuzumab (which targeted brain amyloid) to demonstrate clinical efficacy in late-phase studies in mild to moderate AD dementia. (revised per Amendment 01)

With this consideration taken into account, the primary clinical population of focus in this study is subjects with MCI/Prodromal AD. The mechanism of action of a BACE1 inhibitor where amyloid production is reduced means elenbecestat is more likely to be efficacious (ie, slow disease progression) the earlier in disease progression treatment is started, where limited neurodegeneration has occurred and associated clinical deficits are at a minimum. However, since the effect of BACE1 inhibition along the AD continuum remains to be characterized, elenbecestat will also be evaluated for its profile in mild to moderate stages of AD, in the event data emerge supporting its use beyond MCI/Prodromal AD. Indeed, recent data support the notion of continued progression of amyloid pathology even in these later stages of the disease (Hu, et al., 2015), although at a slower pace, suggesting a positive effect of BACE inhibition and amyloid beta reduction cannot be ruled out even in the later stages of the disease trajectory. Hence, in this study, elenbecestat will be assessed in subjects with disease states ranging from MCI/Prodromal to mild and even moderate AD. (revised per Amendment 01)

As discussed, efficacy is more likely to be observed in subjects with MCI/Prodromal AD but there is the possibility that efficacy will also be evident following administration of an amyloid modifying agents such as elenbecestat in subjects with more advanced disease such as mild to moderate AD. (revised per Amendment 01) For example, a study of tarenflurbil,

a selective Aβ(1-42)-lowering agent, on cognition and function in subjects with mild to moderate AD showed the subjects with mild AD had lower rates of decline than those in the placebo group in activities of daily living and global function; however, slowing of cognitive decline did not differ significantly (Wilcock, et al., 2008). Similarly, differential effects on cognitive measures have been observed with solanezumab, where some benefit from treatment was observed in subjects with mild AD, although studies with solanezumab were considered to have failed to improve cognition or functional ability significantly (Doody, et al., 2014). Therefore, it is relevant to compare the effect of the BACE1 inhibitor elenbecestat in 2 different subject populations that differ in terms of AD severity before the initiation of large Phase 3 clinical studies. (revised per Amendment 01)

### 9.2.3 Rationale for Clinical Endpoints

The 14-item version of the ADAS-cog will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007).

The CDR is a clinical global rating scale requiring the interviewing of both the subject and an informant who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975)

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials on the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson et al., 2011, Lim, et al., 2012a, Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with elenbecestat treatment.

The CBB is a brief, computer-administered cognitive test battery that requires approximately 10 minutes for administration (Darby, et al., 2012; Fredrickson, et al., 2008; Maruff, et al., 2009). The CBB has been used to detect cognitive impairment in several neurodegenerative conditions including the measurement of cognitive function in healthy older adults and in adults with clinically diagnosed AD and prodromal AD (Darby, et al., 2009; Hammers, et al., 2012; Lim, et al., 2012a; Lim, et al., 2012b). The administration, scoring, and reporting of the CBB is automated and highly standardized, resulting in cognitive paradigms that have

been well-validated in neuropsychological and cognitive studies (Fredrickson, et al., 2008; Maruff, et al., 2009). See Section 9.5.1.3.1 for further details.

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression. Volumetric magnetic resonance imaging is discussed in Section 9.2.4.4.

## 9.2.4 Rationale for Biomarkers

### 9.2.4.1 Overall Rationale

The biomarker strategy for this study includes the following aims:

- To establish an amyloid load in the brain at study entry (via the PET eligibility inclusion criterion)
- To evaluate safety (principally by MRI)
- To evaluate a PD effect in terms of both Aβ in CSF and brain amyloid assessed by amyloid PET and to establish that this PD effect is maintained long-term (revised per Amendment 02)
- To evaluate disease modification through longitudinal assessments of vMRI, amyloid PET, and CSF biomarkers of neurodegeneration (t-tau and p-tau)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

### 9.2.4.2 Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect of elenbecestat on Aβ(1-40)+Aβ(1-42) and other C-terminally truncated Aβ peptides such as Aβ(1-38) through inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using [$^{11}$C]PiB, suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases in CSF Aβ concentrations that are seen in AD are believed to be related to this decrease in brain Aβ availability.

Both t-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni and Bhaskar, 2012). CSF tau measurements have been correlated with cerebral atrophy, while their ratios with Aβ42 have provided useful predictors of cognitive decline and progression to dementia due to AD. Rebalancing dysregulated amyloid production early in the process may positively affect the neurodegenerative process

and thus affect these markers and benefit the disease trajectory. Therefore, monitoring these markers in conjunction with amyloid imaging may provide further supportive evidence of disease modifying effects. (revised per Amendment 04)

Baseline levels of Aβ(1-42), t-tau, and p-tau will also help elucidate the extent of AD pathology at entry to the study and can be combined with baseline levels of *ApoE4* genotyping in addition to the baseline imaging variables to help explain differences in treatment response.

The study will be stratified at randomization for *ApoE4* gene status in order to account for any *ApoE* status by treatment interaction or *ApoE* status by amyloid-related imaging abnormalities risk interaction.

#### 9.2.4.3 Amyloid PET

Amyloid PET imaging will be used in this study for 2 primary reasons: 1) to confirm the presence of AD pathology in the brain of subjects with MCI/Prodromal AD or mild to moderate AD at entry to the study; and 2) to evaluate the effects of elenbecestat on amyloid levels in the brain, both by whole brain analysis (the average of 5 to 6 cortical regions) and brain region analysis. (revised per Amendment 01)

Longitudinal amyloid PET imaging will be conducted after 18 months of treatment in the Core Study (or at ED, providing the subject has received at least 39 weeks of study drug) as an exploratory measure of the potential disease-modifying effects of elenbecestat. (revised per Amendment 07) Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses). (Revised per Amendments 02 and 05)

#### 9.2.4.4 vMRI

Volumetric imaging will be used to evaluate the effects of elenbecestat on rates of atrophy across the different dose groups during the Core Study and to provide support that effective treatment is associated with modification of disease course (exploratory endpoints in the Core Study and Extension Phase). (revised per Amendments 01 and 07) A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. Clinically efficacious doses are predicted to be associated with a slowing in the rate of hippocampal atrophy compared with rates observed in the placebo and non-efficacious dose groups. Treatment effects on left and right hippocampal, whole brain, and total ventricular volumes are exploratory endpoints.

Annualized rates of change of 2% to 3% have been reported for the AD brain compared with 1% in MCI and <1% in age-matched controls (Hua, et al., 2010, Leung, et al., 2010). However, subjects with MCI due to AD-dementia (CSF Aβ <192 pg/mL or positive amyloid imaging) show rates of atrophy comparable to those observed in subjects with AD-dementia (Hua, et al., 2009; Hua, et al., 2010; Leung, et al., 2010; Morra, et al., 2009), supporting the

notion that such subjects are on similar trajectories as those with mild AD-dementia. Lower levels of CSF Aβ42, amyloid positivity on PET imaging, and higher levels of CSF t-tau in addition to the presence of the *ApoE4* allele have all been associated with greater rates of brain atrophy (Fjell, et al., 2010a; Fjell, et al., 2010b) and will be entered as covariates in various analyses. Hippocampal atrophy has also been shown to predict clinical progression independently of amyloid levels in the brain (Jack, et al., 2010), and this measure will be entered as a covariate in the analysis of the clinical endpoints along with the aforementioned variables.

Brain volume (total ventricular volume, whole brain, temporal lobe) generally shows a modest correlation with performance on a number of cognitive scales (Hua, et al., 2009; Hua, et al., 2010; Freeborough, et al., 1997; Leung, et al., 2010). Using volumetric analysis performed at 6-month intervals during the Core Study and at Month 24 and Month 48 of the Extension Phase, these relationships and the effects of elenbecestat treatment will be explored further. Subjects who discontinue early from the Extension Phase will have safety brain MRI and vMRI assessments at the ED Visit if these assessments have not already been performed during the preceding 90 days. (revised per Amendments 07 and 08) Recent advances in analysis software have made structural imaging more sensitive to detect small changes and able to reliably measure rates of atrophy at these intervals, particularly in the posterior parietal and the lateral temporal regions during the early stages of disease (Hua, et al., 2009; Hua, et al., 2010). Given these observations, a demonstration of significant slowing or stabilization in the rate of atrophy in response to treatment, compared with placebo, will offer further support for disease modification.

### 9.2.5 Clinical Risks and Mitigation Strategy

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with elenbecestat, and to mitigate clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of Core Study treatment and 48 months of Extension Phase treatment in this Phase 2 study. (revised per Amendments 07 and 08) These safety aspects include the following:

- Immunology-related and infection-related exclusion criteria for both the Core Study and the Extension Phase (revised per Amendment 07)
- Review of unblinded safety data by an independent DSMB at regular intervals
- Safety criteria for study drug discontinuation based on CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cell) during the Core Study and absolute lymphocytes during the Extension Phase (revised per Amendment 07)
- Safety criteria for study drug discontinuation during the Core Study and Extension Phase based on skin rash, reoccurrence of herpes virus infections including any oral herpes, genital herpes or shingles, other infections, MRI changes, ECGs, and pregnancy. (revised per Amendment 07)

In addition to the features above, other safety aspects of this study designed to mitigate clinical risk include the following:

- Blinded safety data will be monitored by Eisai at regular intervals during the course of the Core Study
- Routine safety assessments will include the monitoring and recording of all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and dermatological assessments at regular intervals. (revised per Amendment 07) AEs that might indicate signals of possible drug abuse potential will require a detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events. To assess potential immunomodulatory effects, peripheral blood mononuclear cells (PBMCs) will be collected at baseline, during treatment, and posttreatment of the Core Study and at Extension Phase Baseline (Visit 21), 6 months (Visit 26), 12 months (Visit 28), and 24 months (Visit 32). (revised per Amendment 08)

As per the communication from the FDA in Aug 2013, there are concerns that hypopigmentation of the skin and mucous membranes may occur with BACE1 inhibitory drugs. Although no such effects have been seen with elenbecestat to date, assessments using standardized photography will be performed by a central reviewing dermatologist at regular intervals during the Core Study. During the Extension Phase, a dermatologic assessment will be performed by the investigator at every scheduled visit. Every assessment will specifically include evaluation of any areas of depigmentation or any rash. (revised per Amendment 07) Dermatological assessments will be supplemented with a specific question to subjects regarding skin changes at each visit. Any such changes could be referred to the central reviewing dermatologist, and to a local dermatologist if needed, for further evaluation. See Section 9.5.1.5.8 and Appendix 6 for further details. (revised per Amendment 07)

- Baseline and on-study blood will be taken and stored for all subjects during the Core Study and Extension Phase. (revised per Amendment 02 and 07) DNA samples and CSF samples (for all subjects who consent to CSF sample collection) will be taken and stored during the Core Study. (revised per Amendment 02 and 07) These samples may be tested in the event that a subject develops AEs that warrant further investigation (eg, if a subject develops a treatment-emergent infection) (see Section 9.5.1.2.2 and Appendix 6). (revised per Amendment 07)
- Central reading of safety brain MRI assessments (including any MRI evidence of demyelination) will be performed at Screening, at approximately 6-month intervals during the Core Study Treatment Period, and at the final Follow-up Visit during the Core Study. (revised per Amendment 07) MRI assessments will also be performed at Month 24 and Month 48 of the Extention Phase Treatment Period. Subjects who discontinue early from the Extension Phase will have safety brain MRI and vMRI assessments at the ED Visit if these assessments have not already been performed during the preceding 90 days. In addition, safety brain MRI assessments may be performed as an unscheduled assessment if clinically indicated. (revised per Amendments 07 and 08)

- Full neurologic examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. Details of the neurologic examination are given in Section 9.5.1.5.9 and Appendix 6. (revised per Amendment 07)
- Cognitive decline will be assessed as a safety assessment during the Core Study (ADAS-cog14, MMSE, and CBB) and during the Extension Phase (MMSE). (revised per Amendment 07) Of particular importance will be the assessment of reaction time testing using the detection and identification tasks on the CBB during the Core Study. (revised per Amendment 07)
- During the Core Study, an assessment of suicidality using the C-SSRS will be performed at Screening, Baseline, and at regular intervals during the Treatment and Follow-up Period (see Section 9.5.1.5.11). During the Extension Phase, C-SSRS will be performed at Visit 21 (start of Extension Phase treatment) and at Month 24 and Month 48 of the Extension Phase Treatment Period. Subjects who discontinue early from the Extension Phase will have assessments of suicidality using C-SSRS at the ED Visit. Additional clinical assessments of reported suicidal thinking and behavior will be performed by the investigator during the Extension Phase at visits that do not include administration of C-SSRS (see Appendix 6). (revised per Amendments 07 and 08)
- All subjects, regardless of whether they complete all 18 months of treatment or prematurely discontinue study drug during the Core Study, will have at least 4 off-treatment Follow-up Visits during the Core Study (2, 4, 8, and 12 weeks after the last dose of study drug). Subjects who complete or prematurely discontinue study drug during the Extension Phase will have 2 off-treatment Follow-up Visits at 4 and 12 weeks after the last dose of study drug. (revised per Amendment 07)
- More frequent safety assessments can be made as unscheduled assessments/visits during the off-treatment Follow-up Period, if clinically indicated. (revised per Amendment 04)
- An ophthalmic examination will be conducted at Baseline and if the subject experiences visual disturbances during the course of the Core Study (see Section 9.5.1.2.1).

## 9.3 Selection of Study Population

Approximately 60 (±20%) eligible MCI/Prodromal or mild to moderate AD subjects will be randomized at approximately 35 sites in the United States (revised per Amendments 02 and 04). There will be no restriction to the number of subjects from either population.

Subjects who do not meet all of the inclusion criteria in Section 9.3.1 or who meet any of the exclusion criteria in Section 9.3.2 will not be eligible to receive study drug during the Core Study. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria provided in Appendix 6 will not be eligible to enter the Extension Phase. (revised per Amendment 07)

### 9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD (Albert, et al., 2011) or AD dementia (McKhann, et al., 2011) and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at Screening Visit 1:**

(revised per Amendment 02)

   a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation

   b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT. Alternatively, cognitive impairment of at least 0.5 SD from age-adjusted norms in delayed recall on the ISLT plus impairment of at least 1 SD from age-adjusted norms in at least 1 other computerized learning and memory test (ISLT immediate recall, or 1 of the learning and memory components of the CBB). (revised per Amendment 02)

   c. FAQ ≤24 (revised per Amendment 01)

   d. MMSE ≥16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading; an historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group (revised per Amendment 02)

3. Male or female, age 50 to 85 years, inclusive at time of consent

4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.

5. If receiving acetylcholinesterase inhibitors (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the Baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.

6. Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization

### 9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or MRI
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and <1cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could, in the opinion of the investigator, confound the MCI/Prodromal or mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendments 01 and 02)
7. A score of ≥8 on the 15-item Geriatric Depression Scale (GDS) at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the LLN for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac

pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.

12. Any contraindications to LP for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity). Only applicable to subjects consenting to CSF sample collection (revised per Amendment 02)
13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of Ig deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization
20. Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below population-adjusted LLN at Screening or Baseline and confirmed by a repeat test conducted 1 week after the initial test. The population-adjusted LLN for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are 396, 157, and 74 cells/µL respectively. See Appendix 5. (revised per Amendment 02)
23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the investigator and the medical monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of

clinical immunodeficiency. The discussion with the medical monitor should include a detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)

24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate ECGs. A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute (bpm) at Screening or Baseline
29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.
33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo). Diagnosis of an underlying disease causing hypopigmentation is not necessary for exclusion if the clinical presentation is consistent with such a condition. Hypopigmentation associated with scarring need not be exclusionary. (revised per Amendment 02)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the C-SSRS suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline

Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period or for 28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.
    - Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
    - (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]). (revised per Amendment 04)

### 9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may discontinue study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to stop study drug or withdraw from the study at any time for any reason.

Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). Follow-up Visits will also be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug in the Core Study (see Section 9.1.2.3), and 4 and 12 weeks after the last dose of study drug in the Extension Phase (see Appendix 6). (revised per Amendments 04, 05, and 07)

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the Subject Disposition eCRF page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study drug and withdraws from the study at the same time, the ED Visit will be followed (see Section 9.5.5).

Safety-related criteria for discontinuation of study drug during the Core Study include the following: (revised per Amendments 07)

a. A study drug discontinuation threshold will be set based on absolute counts of CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells). The discontinuation threshold will be set at below the level of the population-adjusted LLN (CD4=396 cells/µL; CD8=157 cells/µL; and CD19=74 cells/µL), at a level that represents a greater risk of opportunistic infection in the treated population. (revised per Amendment 02) For CD4 (T helper cells) the discontinuation threshold is 250 cells/µL. For CD8 (cytotoxic T cells) and CD19 (B cells) the discontinuation thresholds are 150 cells/µL and 50 cells/µL, respectively. Any subject who has CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below the discontinuation threshold as confirmed by a repeat test conducted within 1 week of the initial test but who has no clinical signs or symptoms of infection, will have study drug temporarily suspended for at least 2 weeks but no more than 4 weeks. During this period of study drug suspension, lymphocyte subset counts and complete blood count (CBC) with differentials will continue to be tested weekly until CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) have all returned to greater than the population-adjusted LLN after which time study drug can be resumed. Testing of lymphocyte subset counts and CBC with differentials is required weekly for 4 weeks following resumption of study drug administration. Temporary suspension and rechallenge with study drug is only permitted once for any given subject. If the lymphocytes and CD counts do not return to greater than the population-adjusted LLN within 4 weeks from the start of temporary suspension the subject will need to be permanently discontinued from study drug. (revised per Amendment 04)

b. Subjects with CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between the population-adjusted LLN and the discontinuation threshold will have lymphocyte subset counts performed on a weekly basis. (revised per Amendments 02

and 04) During the early stages of the Treatment Period, where visits are conducted weekly (ie, Visits 4, 5, 6, and 7), lymphocyte subsets are already scheduled to be measured on a weekly basis and so additional visits or blood draws are not required. (revised per Amendment 02) For these subjects, the decision as to whether the subject remains on study drug or is to be discontinued from study drug will be based upon clinical judgment and will take into account any clinical presentation in addition to the lymphocyte subset counts. These subjects may continue with treatment if there is no clinical evidence of infection. They will be discontinued from study drug if they have infections of a moderate to severe intensity (eg, subjects whose infections are not localized, or are systemically unwell, or who require systemic anti-infective drug treatment).

**Table 1 Study Drug Actions for Lymphocyte Subset Absolute Counts**

| Lymphocyte subset absolute counts | Action | Decision to continue, discontinue, or temporarily suspend study drug |
|---|---|---|
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold and no clinical signs or symptoms of infection | Retest within 1 week along with<br>CBC with differentials | If retest performed within 1 week confirms lymphocyte subset counts below the discontinuation threshold, temporarily suspend study drug for between 2 and 4 weeks. Continue weekly testing of lymphocyte subsets and CBC with differentials. Rechallenge with study drug allowed when CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts all greater than population-adjusted LLN. Temporary suspension and rechallenge permitted only once for each subject. |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between population-adjusted LLN and discontinuation threshold | Lymphocyte subset counts (and CBC with differentials) to be performed weekly until lymphocyte subset counts return to ≥ population-adjusted LLN | Decision will be based upon lymphocyte subset counts and clinical judgment |

LLN = lower limit of normal, CBC = complete blood count.

(Table revised per Amendments 02 and 04)

c. Subjects with clinical evidence of infection will have their CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts measured. Blood and other biological samples will also be collected for investigations of infective pathogens (eg, serological tests, quantitative polymerase chain reaction, microscopy, and culture) where appropriate. In subjects with infection, if any of their absolute cell counts meets the discontinuation thresholds, study drug will be discontinued. All subjects with severe

infections will be discontinued from study drug. All subjects with herpes zoster (shingles) or ocular herpes infections will be discontinued from study drug, regardless of severity of presentation. Subjects with mild or moderate infection may continue treatment with study drug unless otherwise clinically indicated or otherwise specified below. Specifically, when any of the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are between the population-adjusted LLN and the discontinuation thresholds, subjects with infections of moderate intensity will be discontinued from study drug (eg, subjects whose infections are not localized, or subjects who are systemically unwell, or who require systemic anti-infective drug treatment). All subjects with infection who are discontinued from study drug will be followed for a period of 12 weeks or until the infection resolves/stabilizes or until the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts have returned to greater than population-adjusted LLN (whichever comes latest). (revised per Amendments 02 and 04)

**Table 2 Study Drug Actions for Lymphocyte Subset Absolute Counts and Infection**

| Criterion | Severity of Infection | | | |
|---|---|---|---|---|
| | None | Mild | Moderate | Severe |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold | If confirmed with repeat testing within 1 week, then temporarily suspend study drug as per instructions above. | Discontinue study drug | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between population-adjusted LLN and discontinuation threshold | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts always > population-adjusted LLN | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated (See (e) for exception) | Discontinue study drug |

LLN = lower limit of normal.

(Table revised per Amendments 02 and 04)

d. A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (see (e) for exception), will be discontinued from study drug and a dermatological consult will be requested regardless of whether the rash is considered drug-related or due to other causes. For cases where the investigator

suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatological consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

e. Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

f. Development of any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. If discontinued from study drug, subjects will undergo an ED Visit within 7 days after discontinuation and will attend the Follow-up Visits 2, 4, 8, and 12 weeks after the last dose of study drug. They will also undertake an UNS Visit (with MRI) at approximately 4 weeks after the visit at which such MRI features were first identified. An MRI will also be performed at approximately the time of the final Follow-up Visit (Visit 20). Additional visits for safety may be arranged if clinically indicated in the opinion of the investigator, including after 12 weeks after the last dose of study drug. At any time during the Treatment Period, subjects who have asymptomatic, treatment-emergent microhemorrhages as detected by MRI, but none of the features which merit discontinuation of treatment (ie, vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic treatment-emergent microhemorrhage) may continue with treatment. These subjects will have safety assessments (including MRI) at approximately 4 weeks after the visit at which such MRI features were found. They will also continue with the scheduled MRI scans. Additional unscheduled MRI scans may be arranged on an individual subject basis in discussion with the study medical monitor. (revised per Amendment 04)

g. A postdose ECG with an average QTcF interval >500 msec from triplicate ECGs

h. A postdose ECG with a QTcF interval increase from baseline >60 msec and a QTcF interval >450 msec as demonstrated from triplicate ECGs

i. Any seizure (motor or non-motor)

j. Pregnancy

Safety-related criteria for discontinuation of study drug during the Extension Phase are provided in Appendix 6. (revised per Amendment 07)

## 9.4 Treatments

### 9.4.1 Treatments Administered

For the Core Study, the test drug is elenbecestat and the control drug is placebo. (revised per Amendments 07) All study drugs are to be administered orally, QD, with food.

Treatments to be administered during the Core Study are 5, 15, and 50 mg elenbecestat or placebo before the implementation of Amendment 06, and 50 mg elenbecestat or placebo after the implementation of Amendment 06 as shown in Figure 1. (revised per Amendments

01, 05, 06, and 07) Study treatment will begin on Day 1 (at the study site) following Randomization and will continue for approximately 78 weeks. Please refer to Table 7 and Section 9.5.1.4.1 for specific information on drug administration on days when PK sampling is to be performed.

Treatments to be administered during the Extension Phase are described in Appendix 6. (revised per Amendment 07)

Study drug doses will remain the same for each individual subject unless the interim PK/PD analysis determines that an entire dose level requires adjustment (Section 9.4.4). See Section 9.3.3 for safety-related discontinuation criteria of study drug. If a subject develops a concurrent illness during the Treatment Period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

### 9.4.2 Identity of Investigational Product

Elenbecestat (E2609) tablets of 5-, 10-, and 25-mg dose strengths will be supplied. Placebo tablets of identical appearance will also be available. Each subject will receive 2 tablets, which combined will make up the required doses of elenbecestat 5, 15, 50 mg, or placebo. The tablets will be supplied by the sponsor in labeled blister packs. The product-release certificates for elenbecestat and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either elenbecestat or placebo, or both (see Section 9.4.2.3 for labeling details).

#### 9.4.2.1 Chemical Name and Formula of Elenbecestat (E2609)

- Test drug code: E2609
- Generic name: Elenbecestat
- Chemical name: International Union of Pure and Applied Chemistry
- *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

#### 9.4.2.2 Comparator Drug

Not applicable.

#### 9.4.2.3 Labeling for Study Drug

Elenbecestat will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier (ID)
- Lot number/batch number
- Storage conditions, expiration date if necessary

#### 9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

### 9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups are described in Section 9.4.1. (revised per Amendments 01 and 05)

Randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized blister card identification numbers. At enrollment, the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 3), the IxRS will assign each subject a unique randomization number.

### 9.4.4 Selection of Doses in the Study

It is not known how the level of CSF or brain Aβ reduction is related to clinical efficacy. Therefore, in this study, initial doses will be selected such that at steady state, they will result in 25%, 50%, and 75% reduction in CSF Aβ levels from baseline to cover a broad range of PD effects. (revised per Amendment 06)

In Study 007, the relative bioavailability of a tablet formulation of elenbecestat in the fed and the fasted states compared with the capsule formulation in the fasted state (used in Studies 001 and 002) was investigated. It was found that when the tablet form of

elenbecestat (50 mg) was administered with food, the exposure (ie, AUC) of the parent drug elenbecestat was higher, with lower maximum observed concentrations and reduced exposure to the metabolites, compared with either formulation in the fasted state.

Based on the PK/PD modeling using data from healthy volunteer Studies 001, 002, and 007, doses of 5, 15, and 50 mg QD administered as the tablet formulation with food in the Core Study should achieve CSF Aβ reduction from baseline of approximately 25%, 50%, and 75% at steady state, respectively (Table 3).

**Table 3 Predicted Steady State Plasma PK Parameters and CSF Amyloid β Reduction From Baseline**

| Elenbecestat Tablet Daily Dose (mg) With Food | Plasma Elenbecestat | | | % Reduction CSF BACE1 Activity | % Reduction CSF Aβ(1-x) |
|---|---|---|---|---|---|
| | $C_{max,ss}$ (ng/mL) | $C_{ss,av}$ (ng/mL) | $AUC_{(0-24h)ss}$ (ng·h/mL) | | |
| 5 | 6.2 | 3.3 | 80.3 | 16.2 | 33 |
| 15 | 18.6 | 10 | 240.9 | 36.6 | 56 |
| 50 | 62.1 | 33.5 | 803.0 | 65.7 | 79 |

Aβ(1-x) = amyloid beta monomer from amino acid 1 to x, $AUC_{(0-24h)ss}$ = area under the concentration x time curve at steady state from time zero to 24 hours, BACE1 = beta-amyloid converting enzyme, CSF = cerebrospinal fluid, $C_{ss,av}$ = average steady-state concentration, $C_{max,ss}$ = maximum plasma concentration at steady state, PK = pharmacokinetics.

The PK/PD modeling described above, which was conducted using data obtained from healthy volunteers, has also been supported by modeling of data from subjects with an underlying AD pathology (Study 101). Furthermore, external data with another BACE1 inhibitor (MK-8931) showed a similar PD effect in AD patients as in healthy volunteers (Forman, et al., 2013). Therefore we are confident that the modeling of elenbecestat effects in healthy subjects will be applicable for both MCI/Prodromal and mild to moderate AD dementia patients. (revised per Amendment 01)

The exposure of the highest dose in the Core Study (50 mg QD tablet administered with food) is less than that of the 100 mg QD dose (capsule administered fasted) in Study 002.

The 100 mg QD dose administered for 14 days in Study 002 was well tolerated with no clinically significant changes in laboratory parameters, vital signs, or ECG parameters. On Day 15, for the 100 mg QD cohort in Study 002, there was a reduction of CD4 lymphocyte counts compared with placebo (CD4 lymphocyte counts on elenbecestat decreased by 3.1% from baseline, whereas the placebo control showed an increase of 8.7%), but this decrease was less than that observed at doses of 200 mg (22.9% decrease) or 400 mg (17.3% decrease). No subject had infections or drug rash while receiving elenbecestat 100 mg QD or at lower doses in Study 002, whereas at 200 and 400 mg QD, 4 subjects had symptomatic orolabial HSV1 relapses and 2 subjects at the highest dose had drug rash. The highest dose for Study 202 of 50 mg QD (tablet administered with food in the Core Study) is therefore expected to have a similar or better safety profile compared with the 100 mg QD capsule (administered fasted) in Study 002. Specific exclusion criteria, blinded and unblinded safety monitoring procedures, and safety criteria for discontinuation from

study drug are included in this study in order to mitigate any immunology-related risk with elenbecestat, particularly in light of the progression from 14 days of dosing (Study 002) to 18 months of dosing in this study.

Interim analyses of the elenbecestat plasma PK for all subjects and the elenbecestat CSF PK and PD profiles will be performed on baseline data and samples collected after at least 4 weeks of treatment. These interim analyses, as well as analyses of safety data, will be performed on an ongoing basis. Refer Section 9.7.3 for more detail. The median and mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment for each dose of elenbecestat and its 90% CI for the median will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data and will relate the average steady state plasma concentration of elenbecestat to steady state CSF Aβ(1-x) percentage reduction from baseline after at least 4 weeks of dosing. (revised per Amendments 01, 02, 03, 04, and 05)

Unblinded interim analyses have indicated elenbecestat 50 mg per day produced relatively high levels of CSF Aβ reduction (greater than 50%) with an acceptable safety profile. As a result, elenbecestat 50 mg has been selected as the dose for Phase 3 development. To gain a more comprehensive safety and tolerability profile of elenbecestat 50 mg, subjects randomized to elenbecestat 5 and 15 mg will be re-assigned to elenbecestat 50 mg for the remaining of the 18-month Treatment Period with the provision that they will have at least 12 weeks of treatment remaining in the Randomization Phase. (revised per Amendment 06)

### 9.4.5 Selection and Timing of Dose for Each Subject

Elenbecestat is administered orally, QD, with food in the Core Study. Study treatment will begin on Day 1 following randomization and will continue for approximately 78 weeks.

### 9.4.6 Blinding

Elenbecestat and placebo will be administered as tablets of identical appearance during the Core Study.

During the Randomization Phase and Follow-up Phase in the Core Study, subjects, caregivers/informants, and all clinical site personnel involved with the conduct and interpretation of the study, including investigators will be blinded to the treatment codes (double-blind). In order to make decisions about the remainder of the study as well as the full elenbecestat clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. (revised per Amendment 03)

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (ie, those who are trained and certified to perform the various cognitive assessments that are undertaken in this study). Furthermore, at the site, the notes and reports relating to safety assessments must be kept separate from the notes and reports relating to efficacy, particularly for the CDR. (revised per Amendment 01)

Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

The PK/PD interim analyses will take place throughout the study as per Amendment 03 and will be conducted by an independent PK/PD scientist at the sponsor. Any additional changes to dose required for this study will be reflected in a further amendment to the protocol and the Statistical Analysis Plan will detail how data will be handled in the primary analysis. (revised per Amendments 02 and 04)

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

At the conclusion of the study, all unused drug supplies are to be returned to the Eisai approved contract packaging vendor.

### 9.4.7 Prior and Concomitant Therapy

Medication (including over-the-counter medications) or therapy administered to the subject before the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs during the Core Study and Extension Phase are provided in Appendix 2. (revised per Amendment 07) Prohibited medications are presented in Listing 1 through Listing 5. Medications that are permitted with restrictions are listed in Listing 6 through Listing 8. (revised per Amendment 04)

The types of agents listed below are not permitted before randomization unless discontinued according to the specific timeframes as shown below; these types of agents are not permitted during the Core Study or Extension Phase until after the last treatment visit: (revised per Amendments 04 and 07)

- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines

- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization. However, during the Treatment Period of the study, short term (not more than 14 days) use of steroids up to the equivalent of prednisolone 40 mg QD is permitted after discussion with the medical monitor. Dosing with study drug should be suspended from the time steroid treatment is started. Complete blood count and lymphocyte subsets (for Core Study and first 12 months of Extension Phase only) should be determined before starting steroid treatment and continue to be monitored weekly. (revised per Amendment 08) Study drug may be resumed after discussion with the medical monitor when the following conditions are met: (1) treatment with steroids has been completed for at least 1 week; (2) absolute lymphocytes not <LLN; (revised per Amendments 07) (3) no lymphocyte subsets are below the discontinuation threshold (for Core Study only); (4) the investigator considers that the medical condition which required treatment with steroids has improved or resolved. Weekly testing of lymphocyte subset counts (for Core Study only) and CBC with differentials (for Core Study and Extension Phase) is required for 4 weeks following resumption of study drug administration. (revised per Amendment 04)
- (revised per Amendment 06)

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for any efficacy analyses. (revised per Amendment 05)

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed. Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before randomization. They may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 04)
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety, and are not prohibited above. (revised per Amendment 05)

Antiplatelet therapy: (revised per Amendment 04)

- For subjects who consent to CSF sample collection: Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) are permitted in all subjects. Aspirin and

clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

- For subjects who do not consent to CSF sample collection: Aspirin and clopidogrel, individually or in combination, are permitted.

### 9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period. Clinical research associates will review treatment compliance during site visits and at the completion of the study.

### 9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the principal investigator including a copy of the principal investigator's current medical license (required for United States sites) or medical registration number on the curriculum vitae
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

## 9.5 Study Assessments

### 9.5.1 Assessments

#### 9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

#### 9.5.1.2 Baseline Assessments

Assessments to be made at Screening and Baseline and throughout the study are described in Section 9.5.1.3, Section 9.5.1.4, and Section 9.5.1.5.

##### 9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, current medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment due to AD. Subjects will be asked about history of TB, infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV Types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include onset, duration, relapse frequency, severity, and treatments. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The 15-item GDS and modified Hachinski ischemic scale will also be assessed at Screening as part of the exclusion criteria.

Physical examinations (complete or routine) will be performed as designated in Table 6, Table 7, and Table 14. (revised per Amendment 07) A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, and skin, and a neurological examination (including the Brief Smell Identification Test [Sensonics Inc.]). (revised per Amendment 04). A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

##### 9.5.1.2.2 VIRAL TESTING

As specified in Table 6, blood will be collected for screening for Hepatitis B and Hepatitis C for determining eligibility, and at Baseline for viral characterization.

##### 9.5.1.2.3 B12 TESTING

Blood will also be collected for vitamin B12 levels as specified in Table 6.

#### 9.5.1.2.4 TB EXPOSURE TESTING

Blood will also be collected for testing for previous TB exposure, as specified in Table 6.

#### 9.5.1.2.5 URINE DRUG TESTING

Urine will be collected for drug screening as specified in Table 6.

### 9.5.1.3 Efficacy Assessments

#### 9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

The timing of psychometric assessments is shown in Table 6, Table 7, and Table 14. (revised per Amendment 07) These assessments should be administered in the morning (or, if not possible, consistently at the same time of day) and should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). At the Screening Visit, the recommended order of assessments is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. At the Baseline Visit, the assessments are to be conducted in the following order: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). (revised per Amendment 02)

At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

**Alzheimer's Disease Assessment Scale - cognitive subscale:** Discussed in Section 9.2.3. (revised per Amendment 05)

**Clinical Dementia Rating:** The CDR assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

**Mini Mental State Examination:** A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

**ISLT:** The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects will read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 15 minutes, in which time the CBB is performed, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

**CogState Brief Battery:** The CBB is a computer-based battery comprising 4 cognitive tests:

- Detection – a simple reaction time test where the subject presses a key when the card is turned face up from a pack of cards ("Has the card turned over"). Speed of response is the measure.
- Identification – a simple choice reaction time test where the subject presses 1 of 2 keys when the card just turned face up is either a red card or a black card ("Is the card red"). Speed of response is the measure.
- One Card Back – a simple working memory test where the subject presses 1 of 2 keys when the card turned face up is either the card seen in the immediately previous trial or not ("Is the previous card the same"). Accuracy of response is the measure.
- One Card Learning – a visual learning and memory test where the subject presses 1 of 2 keys depending on whether the card just turned face up has been seen before or not in the task ("Have you seen this card before in this task"). Accuracy of response is the measure.

**Functional Assessment Questionnaire:** The caregiver or informant provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent). (revised per Amendment 04)

#### 9.5.1.3.2 VOLUMETRIC MRI

Volumetric MRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the Alzheimer's Disease Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

Volumetric MRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. Volumetric MRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. Volumetric MRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 6, Table 7, and Table 14 according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. (revised per Amendment 07) Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

For subjects who consent to CSF sample collection, CSF samples will be collected by LP (gravity drip method) at the timepoints specified in Table 6 and Table 7 (revised per Amendment 02). The CSF sample taken at the Baseline Visit will only be performed after subjects consent to CSF sample collection, and after confirmation of an amyloid positive PET scan (revised per Amendment 02). See Section 9.5.1.4.2 for further details.

### 9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

#### 9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of elenbecestat. For subjects who consent to CSF sample collection, CSF samples will be collected for the determination of elenbecestat concentrations. (revised per Amendment 02) Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with elenbecestat.

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 6 and Table 7. Two PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visits 5, 11, 14, and 16, and 4 to 8 hours postdose at Visit 7 and Visit 18 (or at the ED Visit). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug with food (in the Core Study) at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or at the ED Visit) the PK blood sample should be collected shortly before or shortly after completing the LP. (revised per Amendment 01) Although the PK sampling procedures at the ED visit should follow those of Visit 18, in the event that study drug has already been discontinued before the ED visit, then no dosing will be conducted. However, a PK sample at trough (before LP) will be collected, followed by LP at approximately the same time as previous visits. A 2nd PK blood sample will be collected as close as possible in time to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

Blood will also be drawn where possible at the 1st report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

#### 9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

**Biomarkers**

Subjects who consent to CSF sample collection will be encouraged to stay at the site after completion of LP for medical observation (revised per Amendment 02). At Baseline, a CSF sample will be collected by LP (gravity drip method) after fasting (preferred), or at least 2 hours after the most recent meal (Section 9.5.1.3.3). The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 [or later postrandomization timepoint] and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. (revised per Amendment 04) At visits where cognitive tests are also performed, if the tests are to be performed on the same day, the LP must be performed after the cognitive tests have been completed and the subjects should rest and drink some fluid to hydrate before the LP. (revised per Amendment 01) The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. The CSF sample will be used for PD assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 levels and activity. (revised per Amendment 04)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The pre- and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendment 04) BACE1 levels will be measured using internally developed fluorescence resonance energy transfer and ELISA based assay(s). Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

The blood sample collected for PD analyses at Baseline should be collected on the same day shortly before or shortly after completing the LP at Baseline. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

At the Baseline Visit, blood samples will be collected and stored for determination of prior exposure to any suspected infective agents in the event that the subject develops treatment-emergent AEs that warrant further investigation (eg, treatment-emergent infection). For subjects who consented to CSF sample collection, CSF samples from the Baseline Visit will also be stored for the same purpose. (revised per Amendment 02) Testing may include,

but not be limited to, serological tests, viral titer by quantitative polymerase chain reaction, or human leukocyte antigen genotyping.

Blood samples will be collected for PD assessments as specified in Table 6, Table 7, and Table 14. (revised per Amendment 07)

For all subjects, baseline and on-study blood samples, DNA samples, and any CSF samples collected from subjects who consent to CSF collection will be stored for up to 15 years. (revised per Amendment 02)

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

**Pharmacogenomics**

A blood sample will be obtained at Baseline and will be used to determine the *ApoE* genotype (homozygous or heterozygous E4 versus non-E4) and the *NAT2* phenotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response, safety, or PK of elenbecestat. Details of which genotype/phenotype data will be applied to the analyses of efficacy, safety or PK will be discussed in the Statistical Analysis Plan.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in elenbecestat exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

**Amyloid PET**

An amyloid PET scan will be performed at Screening to confirm deposition of amyloid in the brain. An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02) Longitudinal amyloid PET imaging will also be conducted after 18 months of Core Study treatment (or at the Core Study ED Visit if the subject has received study drug for at least 39 weeks). (revised per Amendment 07) Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses) (Table 6). (revised per Amendments 02 and 05) PET scanning will be performed with a locally approved Aβ imaging agent (eg, Amyvid). Descriptions and detailed instructions for all imaging can be found in the imaging manual.

Amyloid PET imaging is an exploratory measure of the potential disease-modifying effects of elenbecestat.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, lymphocyte subsets, Igs, and urine values; periodic measurement of vital signs and ECGs; performance of physical and neurological examinations; centralized dermatological assessments; the C-SSRS; and safety MRIs as detailed in Table 6, Table 7, and Table 14 will also be conducted. Additionally, during the Extension Phase, clinical assessment of suicidal thinking and behavior will be conducted only at visits that do not include administration of the C-SSRS; a positive suicidality assessment from the subject or the caregiver/informant on the clinical assessment of suicidality (ie, a "yes" response on the clinical assessment of suicidal thinking and behavior) will trigger the C-SSRS to be administered. Peripheral blood mononuclear cells (PBMCs) will be collected for exploratory immunomodulatory and immune-based analyses at Baseline, during treatment, and posttreatment period of the Core Study and at Extension Phase Baseline (Visit 21), 6 months (Visit 26), 12 months (Visit 28), and 24 months (Visit 32). (revised per Amendments 07 and 08)

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (see Section 9.4.6). (revised per Amendment 01)

##### 9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is elenbecestat.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: It is not necessary to report every sign or symptom as a separate AE if the overall disease [diagnosis] is being reported as an AE.)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, discontinuation of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit during the Core Study (Visit 20, as shown in Table 7, for subjects who do not enter the Extension Phase) or the last Visit during the Extension Phase (Follow-up Week 12 Visit as shown in Table 14, for subjects who participate in the Extension Phase). (revised per Amendment 07) Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF. SAEs will be collected for 3 months after the last dose of study drug, (ie, through to the final Follow-up visit [Visit 20 for subjects who do not enter the Extension Phase or Follow-up Week 12 Visit for subjects who participate in the Extension Phase]). (revised per Amendments 04, 05, and 07)

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the ADAS-cog14, MMSE, ISLT and CBB (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 4.

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis

- Dissociative state

It is the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.11 for a description of the C-SSRS and of the clinical assessment of suicidality). (revised per Amendment 08)

The following AEs will require the collection of information sufficient to provide a detailed description of the event, treatment and outcome to the medical monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection; any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); treatment-emergent depigmentation/hypopigmentation/vitiligo/loss of hair color; amyloid-related imaging abnormalities (cerebral vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a "yes" answer to any suicidality assessment on the C-SSRS or a positive suicidality assessment on the clinical assessment of suicidality (ie, a "yes" response on the clinical assessment of suicidal thinking and behavior). (revised per Amendment 08)

All AEs must be followed through the final Follow-up Visit (Visit 20 for subjects who do not enter the Extension Phase or Follow-up Week 12 Visit for subjects who participate in the Extension Phase), or until resolution, whichever comes first. (revised per Amendments 07 and 08) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. (revised per Amendment 04)

**Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.**

### Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

| | |
|---|---|
| Mild | Discomfort noticed, but no disruption of normal daily activity |
| Moderate | Discomfort sufficient to reduce or affect normal daily activity |
| Severe | Incapacitating, with inability to work or to perform normal daily activity |

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

## Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

*Classification of Causality*

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

#### 9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reportable using the criteria of important medical event if the event does not meet other serious criteria: new onset seizures, ocular herpes.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the eCRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

#### 9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 4. Subjects should be in a seated or supine position during blood collection. Table 6, Table 7, and Table 14 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study. (revised per Amendment 07)

See Section 9.3.3 for safety criteria for discontinuation from study drug-related to absolute counts of CD4, CD8, and B lymphocytes, and for lymphocyte subset counts. See Appendix 6 for safety criteria for discontinuation from study drug related to absolute lymphocyte counts.

## Table 4 Clinical Laboratory Tests

| Category | Parameters |
|---|---|
| **Hematology** | Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils).<br><br>PT, PTT, and INR (Screening, Baseline, and Visit 21 only) (revised per Amendment 02 and 07) |
| **Chemistry** | |
| **Electrolytes** | Bicarbonate, calcium, chloride, phosphate, potassium, sodium |
| **Liver function tests** | Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin |
| **Renal function tests** | Blood urea/blood urea nitrogen, creatinine |
| **Other** | Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid |
| **Urinalysis** | Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells |
| **Other** | Lymphocyte T and B cell subset analyses (see Table 5). Regulatory T cells (revised per Amendment 04)<br>PBMCs (revised per Amendment 02)<br>Ig analyses (IgG, IgA, and IgM).<br>Viral screen (HCVAb [Hepatitis C] and HbsAg [Hepatitis B]).<br>Viral characterization (including HSV1, HSV2 and CMV, etc.)<br>Serum pregnancy test (females of child bearing potential only)<br>Tuberculosis Interferon Gamma Release Assays<br>Tests for thyroid function (thyroid stimulating hormone, free triiodothyronine and free thyroxin) and vitamin B12<br>Blood sample for storage for subsequent testing of immune status<br>Cerebrospinal fluid sampling |

Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials must also be repeated. (revised per Amendment 02)

CMV = cytomegalovirus, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV = herpes simplex virus, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PT = prothrombin time, PTT = partial thromboplastin time.

The 8 different surface markers (including but not limited to CD3, CD4, CD8, CD45, CD19, CD16, CD56, and CD14) and absolute lymphocyte counts will be measured in order to provide the lymphocyte subset data as shown in Table 5. In addition, Regulatory T cells will be measured. Current sponsor data supports the literature showing there is an age-related decline in lymphocyte subsets (see Appendix 5). These data have been used to revise the LLNs for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts to the population-adjusted LLNs of 396, 157, and 74 cells/µL, respectively) (revised per Amendments 02 and 04).

**Table 5 Lymphocyte Subtypes Inclusive in BD Trucount™**

| Cell Type | Cell Surface Markers |
|---|---|
| T lymphocytes | CD3 |
| T helper cells | CD3+, CD4 |
| Cytotoxic T cells | CD3+, CD8 |
| Mature B cells | CD3-, CD19 |
| Natural killer cells | CD3-, CD16, CD56 |
| Macrophages | CD14 |

(Table 5 revised per Amendment 04)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the case report form [CRF] Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

#### 9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [bpm], respiratory rate [per minute], body temperature [in centigrade], and weight [kg]) will be obtained at the visits designated in Table 6, Table 7, and Table 14 by a validated method. (revised per Amendment 07) Measurements of sitting BP and heart rate will be obtained. All BP measurements should be performed on the same arm, preferably by the same person.

#### 9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination will be performed at Screening as described in Section 9.5.1.2.1. At Baseline and during the Randomization Phase, routine physical examinations will take place as shown in Table 7 and Table 14. (revised per Amendment 07) These examinations will include the cardiovascular system, respiratory system, and neurological system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 6, Table 7, and Table 14. (revised per Amendment 07) During the Core Study, 12-lead standard ECGs will be recorded

in triplicate (1 minute apart) after subjects have been resting in the supine position for at least 5 minutes. During the Extension Phase, a single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF is greater than 450 msec on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. (revised per Amendment 07)

On any study day when ECG, vital signs, and blood samples are taken, these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.7 SAFETY MRI

Safety brain MRI assessments will be performed at the times shown in Table 6, Table 7, and Table 14. (revised per Amendment 07) Additional safety MRI scans can be performed at UNS Visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Safety MRIs will be acquired using a standardized procedure that will include fluid-attenuated inversion recovery (FLAIR), gradient-echo, T1, and diffusion-weighted sequences to determine the presence of focal lesions including, but not limited to, evidence for ischemic and hemorrhagic stroke, subdural hematoma, neoplasm, arteriovenous malformation, micro and macrohemorrhages, superficial siderosis, lacunar infarcts, white matter abnormalities, and vasogenic edema. The imaging sequence for the Screening/safety MRI will include: T2 weighted anatomic MRI to rule out major white matter changes, cerebral infarction or other structural lesions, and a high-resolution 3D T1-weighted scan with isotropic voxels with volumes of 1 $mm^3$ or less. In addition, both FLAIR for the detection of vasogenic edema and T2 Gradient Recall Echo for the detection of microhemorrhages will be acquired. The 3D dataset will be reconstructed in transverse slices in Digital Imaging and Communications in Medicine format. The results of this MRI assessment will also be used as the Baseline Period MRI, against which changes after drug administration will be compared. Further details of the MRI protocol can be found in the Imaging Acquisition Guideline. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, 18, 20, 32, and 38. (revised per Amendments 04, 07, and 08) In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. (revised per Amendment 08)

At any time during the Treatment Period, subjects will be discontinued from study drug if they develop any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. All of these features must be reported as study specific AEs (or AEs of special interest). These subjects will undergo an ED Visit within 7 days after study drug discontinuation as well as 4 Follow-up Visits at 2, 4, 8 and 12 weeks after the last dose of Core Study treatment or 2 Follow-up Visits at 4 and 12 weeks after the last dose of Extension Phase treatment. (revised per Amendments 04 and 07) Subjects will also undertake an UNS Visit (with MRI) at approximately 30 days after the visit at which such MRI features were first identified. Additional visits may be arranged if clinically indicated in the opinion of the investigator, and may occur later than 12 weeks after the final dose of study drug.

#### 9.5.1.5.8 DERMATOLOGIC ASSESSMENT

During the Core Study, centralized skin assessments, using standardized photography, will be performed by a reviewing dermatologist at the times shown in Table 6 and Table 7. During the Extension Phase, all dermatologic assessments will be performed by the investigator at the times shown in Table 14. (revised per Amendment 07) All assessments will specifically include evaluation of any areas of depigmentation or any rash.

In addition, subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregiver or informants will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or infection, and the investigator will be required to review such AEs as soon as possible and consider an unscheduled physical and dermatological evaluation. Detailed characteristics of any skin rashes will be captured in the clinical database. Physical examination may be undertaken where indicated. Treatment-emergent abnormal dermatological findings should be reported as AEs.

#### 9.5.1.5.9 NEUROLOGIC EXAMINATION

Neurological examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations as shown in Table 6, Table 7, and Table 14. (revised per Amendment 07) Details of these examinations will be captured in an eCRF. The neurological examinations will monitor for new symptoms and signs which will then alert the investigator to consider new CNS pathology (especially slowly-evolving neurological conditions that may not lead to prominent symptoms). Examples of neurological signs that may indicate new CNS pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. In such a situation, the investigator should consider (but not limited to) demyelination in the differential diagnoses, and should discuss with the sponsor's medical monitor further

investigations or treatment, which will be decided case by case. Neurological examinations will also include the assessment of cranial nerve function, especially the olfactory nerve; the Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits to objectively test olfaction. Treatment-emergent abnormal neurological findings should be reported as AEs.

#### 9.5.1.5.10 PREGNANCY TEST

At Screening and Visit 21, females of childbearing potential will have a serum pregnancy test. At Baseline and during the Treatment Period, urine samples will be obtained from females of childbearing potential for pregnancy tests (see Table 7 and Table 14). (revised per Amendment 07)

#### 9.5.1.5.11 COLUMBIA SUICIDE SEVERITY RATING SCALE

An assessment of suicidal ideation and behavior using the C-SSRS will be performed at the designed time points in Table 6, Table 7, and Table 14. During the Extension Phase, a more general clinical assessment by the investigator, involving both the subject and the caregiver/informant, will be conducted at visits that do not include administration of the C-SSRS. A positive suicidality assessment from the subject or the caregiver/informant on the clinical assessment of suicidality (ie, a "yes" response on the clinical assessment of suicidal thinking and behavior) will trigger the C-SSRS to be administered. A "yes" answer to Type 4 or 5 suicidal ideation or a "yes" response to any suicidal behavior queries will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the medical monitor. (revised per Amendments 07 and 08)

#### 9.5.1.5.12 BIOMARKER SAMPLES

As noted in Section 9.5.1.4.2, CSF (for subjects who consent to CSF sample collection), blood, and DNA samples will be collected and may be used for exploratory biomarker analyses, as well as tested in the event that a subject develops AEs that warrant further investigation. (revised per Amendment 02)

#### 9.5.1.5.13 OPHTHALMIC EXAMINATIONS

An ophthalmic examination will be conducted at Baseline (unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available). An additional examination will be conducted, if the subject experiences visual disturbances during the course of the study or is medically indicated. The ophthalmic examinations should include fundoscopy to look at the optic disc, macula and the rest of the retina, as well as an assessment of visual acuity and visual fields.

### 9.5.2 Schedule of Procedures/Assessments

The Schedule of Procedures/Assessment is described in this section for the Core Study only. The Schedule of Procedures/Assessment for the Extension Phase is provided in Appendix 6, Table 14. (revised per Amendment 07)

#### 9.5.2.1 Schedule of Procedures/Assessments

Table 6 presents the Schedule of Procedures/Assessments for the Core Study Prerandomization Phase. Screening assessments will be organized into 4 tiers (see below and Figure 2). Table 7 presents the Schedule of Procedures/Assessments for the Core Study Randomization Phase.

**Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)**

| Phase | Prerandomization | |
|---|---|---|
| Period | Screening | Baseline |
| Visit | 1 | 2 |
| **Procedures/Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)** | | |
| Informed consent (subject and caregiver or informant) | X (Tier 1) | |
| Subject informed consent for CSF sample collection (voluntary)[a] | X | X |
| Demographics | X (Tier 1) | |
| Medical history[b] | X (Tier 1) | |
| Prior/concomitant medications[c] | X (Tier 1) | X |
| Vital signs including weight[d] | X (Tier 1) | X |
| Height | X (Tier 1) | |
| Complete physical examination | X (Tier 1) | |
| Routine physical examination | | X |
| CBB and ISLT[e] | X (Tier 1) | X |
| MMSE[e] | X (Tier 1) | X |
| CDR[e] | X (Tier 1) | X |
| FAQ[e] | X (Tier 1) | X |
| ADAS-cog14[e] | | X |
| 15-item Geriatric Depression Scale | X (Tier 2) | |
| Modified Hachinski ischemic scale | X (Tier 2) | |
| C-SSRS | X (Tier 2) | X |
| 12-lead ECG[f] | X (Tier 2) | X |
| Blood and urine for clinical laboratory tests[g] | X (Tier 2) | X |
| Blood for lymphocyte subset analyses[h] | X (Tier 2) | X |
| Blood for Ig analyses[i] | X (Tier 2) | X |
| Blood for viral screen[j] | X (Tier 2) | |
| Blood for thyroid function tests[k] | X (Tier 2) | |
| Blood for vitamin B12 test | X (Tier 2) | |
| Test for previous TB exposure | X (Tier 2) | |
| Urine drug screen | X (Tier 2) | |
| Serum pregnancy test (females of childbearing potential only) | X (Tier 2) | |
| Urine pregnancy test (females of childbearing potential only) | | X |
| Safety and Volumetric MRI[l] | X (Tier 3) | |
| Amyloid PET scan[m] | X (Tier 4) | |

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

| Phase | Prerandomization | |
|---|---|---|
| Period | Screening | Baseline |
| Visit | 1 | 2 |
| **Procedures/Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)** | | |
| Inclusion and Exclusion criteria | X (All tiers) | X |
| Adverse events | X (All tiers) | X |
| CSF sampling for PK, PD and storage[a] | | X |
| Blood sample for PK assessments[n] | | X |
| Blood sample for PD and exploratory biomarker assessments[o] | | X |
| Blood sample for pharmacogenomics | | X |
| Blood sample for storage for immune status[p] | | X |
| Blood sample for PBMC isolation | | X |
| Blood sample for viral characterization[q] | | X |
| Centralized dermatological assessment via photography[r] | | X |
| Neurological examinations[s] | | X |
| Ophthalmic assessment[t] | | X |

(Table revised per Amendments 02 and 04)

AChEI = acetylcholinesterase inhibitor, AD = Alzheimer's disease, ADAS-cog14 = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CDR = Clinical Dementia Rating, CMV = cytomegalovirus, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), Ig = immunoglobulin, INR = International Normalized Ratio, ISLT = International Shopping List Task (immediate and delayed recall), LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetics, PET = positron emission tomography, PT = prothrombin time, PTT = partial thromboplastin time, TB = tuberculosis.

Note: Screening assessments/procedures have been organized into 4 distinct tiers. All assessments and procedures in each tier should be completed (see Figure 2), and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures, as long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. Similarly, all screening assessments and procedures must be completed, and eligibility to continue in the study confirmed, before any baseline assessments and procedures commence. Adverse events and eligibility against inclusion and exclusion criteria must be assessed at each stage within the Screening Visit and at the Baseline Visit. (revised per Amendment 01)

Note: All screening and baseline assessments are to be completed within 50 days, plus an additional window of up to 30 days if required (revised per Amendment 02). The interval between availability of the results of the last screening assessment (PET scan) and the first baseline (Visit 2) assessments should be as short as possible and ideally should not exceed 7 days. Visit 3 (Randomization) (see Table 7) should occur no more than 10 days after completion of the Baseline visit (Visit 2) and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion No.20 into account (revised per Amendment 02). Thus, the total Prerandomization Phase may be up to 60 days, plus an additional window of up to 30 days if required (revised per Amendment 02).

a: Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. For those subjects who do consent to CSF sample collection: CSF will be collected by LP after fasting (preferred), or at least 2 hours after the most recent meal. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 [or later postrandomization timepoint] and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. If the LP and cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. The CSF sample will be used for PK and PD assessments. A CSF sample will also be stored for testing in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). (revised per Amendments 01, 02, and 04)

b: To include: mild cognitive impairment and AD history; history of TB, vaccination history against and infections due to varicella zoster virus (chickenpox and herpes zoster or shingles); infections due to HSV1 (orolabial herpes or cold sores) and 2 (genital herpes). Medical history of infections to include: onset, duration, relapse frequency, severity, and treatments. For any active infection within the last 4 weeks before randomization, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)

c: Prior and concomitant medications include AChEIs and memantine, and other medications for cognitive decline.

d: Weight, respiratory rate, body temperature, and sitting blood pressure and heart rate will be obtained.

e: To be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). At the Screening Visit, the recommended order of assessments is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. At the Baseline Visit, the assessments are to be conducted in the following order: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). (revised per Amendment 02) At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

f: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

g: Clinical laboratory tests consist of hematology (including PT, PTT, and INR), clinical chemistry, and urinalysis.

h: Lymphocyte subsets will include but are not limited to the following cell surface marker assessments: CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cells), CD16/CD56 (natural killer cells) and CD14 (macrophages). Regulatory T cells will also be measured. Viability staining may also be employed. Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials, must also be repeated. (revised per Amendments 02 and 04)

i: Igs to be analyzed include IgG, IgA and IgM.

j: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

k: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxin.

l: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images. MRI will be read by an approved central reader. Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session. (revised per Amendment 01)

m: PET scanning will be performed with a locally approved β-amyloid imaging agent, eg, Amyvid if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. The PET image will be centrally read for the purpose of determining eligibility for inclusion into the study. An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02)

n: The PK blood sample should be collected on the same day shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

o: The PD and exploratory biomarker blood sample should be collected shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

p: A blood sample will be collected at Baseline and stored. This sample may be used for exploratory biomarkers associated with study drug or disease, or in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

q: Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

r: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. See Section 9.5.1.5.8 for further details.

s: To be performed by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. Section 9.5.1.5.9 details what is included in the neurological examination. The Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits and serves as part of the neurological examination. (revised per Amendment 04)

t: An ophthalmic examination will be conducted at Visit 2 unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available. The ophthalmic examination should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| Phase | Randomization | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Period | Treatment | | | | | | | | | | | | | | | | | Follow-Up | | | | |
| Visit[a] | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | ED[b] | W2 | 19[c] | W8 | 20[c] | UNS Visit[d] | Interim Safety Visit |
| Day | 1 | 8 | 15 | 22 | 29 | 43 | 57 | 71 | 85 | 113 | 141 | 183 | 274 | 365 | 456 | 547 | | 561 | 575 | 589 | 631 | | |
| Week | 1 | 2 | 3 | 4 | 5 | 7 | 9 | 11 | 13 | 17 | 21 | 27 | 40 | 53 | 66 | 79 | | 81 | 83 | 87 | 91 | | |
| Weeks elapsed since first dose | 0 | 1 | 2 | 3 | 4 | 6 | 8 | 10 | 12 | 16 | 20 | 26 | 39 | 52 | 65 | 78 | | 80 | 82 | 86 | 90 | | |
| Nominal months elapsed since first dose | 0 | | | | 1 | | 2 | | 3 | 4 | 5 | 6 | 9 | 12 | 15 | 18 | | | 19 | | 21 | | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | | | | |
| Routine physical examination | X | | | | X | | X | | X | | | X | X | X | X | X | X | | X | | X[e] | X | |
| Inclusion and Exclusion criteria | X | | | | | | | | | | | | | | | | | | | | | | |
| Vital signs[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X[e] | X | X |
| Respiratory rate | | | | | X | | X | | X | X | X | X | X | X | X | X | X | | X | | X[e] | X | |
| Weight | | | | | | | | | X | | | X | X | X | X | X | X | | | | X | X | |
| Centralized dermatological assessment via photography[g] | | | | | | | | | X | | | X | X | X | X | X | X | | | | X | X | |
| Neurological examination[h] | | | | | | | | | | | | X | | X | | X | X | | X | | X | X | |
| Ophthalmic examination[i] | | | | | | | | | | | | | | | | | | | | | | X | |
| Concomitant medications[j] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | X | X |
| 12-lead ECG[k] | | | X | | X | | X | | X | | | X | | X | | X | X | | X | | X[e] | X | |
| Clinical biochemistry and urinalysis | | | X | | X | | X | | X | | | X | X | X | X | X | X | | X | | X | X | |
| Complete blood count | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[l] | X |
| Blood samples (lymphocyte subset analyses)[l] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[l] | X |
| Blood samples (Igs)[m] | | | | | X | | X | | X | | | X | | X | | X | X | | X | X | X | X | |
| Blood samples (isolation of PBMCs) | | | X | | | | | | X | | | | | | | | | | | | X | | |
| Urine pregnancy test (females of CBP only) | X[n] | | | | | | | | X | | | X | X | X | X | X | X | | X | | | X | |
| Blood sample (storage for immune status)[o] | | | | | X | | | | X | | | X | | X | | X | X | | X | | X | X | |
| CBB and ISLT[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | | |
| MMSE[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | | |
| CDR[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | | |
| ADAS-cog14[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | | |

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| Phase | Randomization | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | | | | | **Follow-Up** | | | | | |
| **Visit[a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **ED[b]** | **W2** | **19[c]** | **W8** | **20[c]** | **UNS Visit[d]** | **Interim Safety Visit** |
| **Day** | **1** | **8** | **15** | **22** | **29** | **43** | **57** | **71** | **85** | **113** | **141** | **183** | **274** | **365** | **456** | **547** | | **561** | **575** | **589** | **631** | | |
| **Week** | **1** | **2** | **3** | **4** | **5** | **7** | **9** | **11** | **13** | **17** | **21** | **27** | **40** | **53** | **66** | **79** | | **81** | **83** | **87** | **91** | | |
| **Weeks elapsed since first dose** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **10** | **12** | **16** | **20** | **26** | **39** | **52** | **65** | **78** | | **80** | **82** | **86** | **90** | | |
| **Nominal months elapsed since first dose** | **0** | | | | **1** | | **2** | | **3** | **4** | **5** | **6** | **9** | **12** | **15** | **18** | | | **19** | | **21** | | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | | | | |
| FAQ[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | | |
| C-SSRS | | | | | X | | X | | X | | | X | X | X | X | X | X | | X | | X[e] | X | |
| Safety and Volumetric MRI[q] | | | | | | | | | | | | X | | X | | X | X | | | | X | X | |
| Amyloid PET[r] | | | | | | | | | | | | | | | | X | X | | | | | | |
| Telephone contact[s] | | | X | | X | | | | X | | | X | | X | | X | X | | | | | X | |
| Blood samples for PK[t] | | | X | | X | | | | X | | | X | | X | | X | X | | | | | X | |
| Blood samples for PD and exploratory biomarkers[u] | | | X | | X | | | | X | | | X | | X | | X | X | | X | | X | | |
| CSF sampling for PK and PD[v] | | | | | X | | | | | | | | | | | X | X | | | | | X | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[f] | X |
| Sleep/dream questionnaire[w] | | | | | | | | | | | | | | | | | | | | | | X | |
| Randomization | X | | | | | | | | | | | | | | | | | | | | | | |
| Dispense study drug[x] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | | | |

**Footnotes for Table 7**

ADAS-cog14 = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating scale, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), Ig = immunoglobulin, ISLT = International Shopping List Task, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, UNS = unscheduled, W2 = new Week 2 Follow-up Visit, W8 = new Week 8 Follow-up Visit. (revised per Amendment 04)

a: Visit 3 should be conducted no more than 10 days after completion of the Baseline visit (Visit 2) assessments and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion #20 into account. (revised per Amendment 02) A window of ±3 days will be permitted for Visit 4 to 14 inclusive. A window of ±10 days will be permitted for Visit 15 to 18 inclusive. A window of ±3 days will be permitted for the Follow-up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since first dose" at subsequent visits.

b: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-up Visits will be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug (Visit W2, 19, W8, and Visit 20, respectively). (revised per Amendments 04 and 05)

**Footnotes for Table 7**

c: All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 4 posttreatment Follow-up Visits; 2, 4, 8, and 12 weeks after the last dose of study drug (Visits W2, 19, W8, and 20, respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-up Period. (revised per Amendment 04)

d: Unscheduled visits may be conducted at any time that safety or safety MRI data indicate per protocol or as clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

e: Only if clinically significant abnormalities are found at Visit 19 and the investigator considers it necessary to repeat at Visit 20. Clinical biochemistry, urinalysis, CBC, lymphocyte subsets and Igs should always be performed at Visit 20, regardless of clinical significance at the previous Follow-up Visit. (revised per Amendments 02 and 04)

f: Measurements of body temperature and sitting blood pressure and heart rate will be obtained.

g: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. Additional UNS dermatological assessments should be conducted in response to any dermatological AEs of concern (eg, depigmentation, rash, herpetic lesion).

h: Examples of neurological signs that may indicate new central nervous system pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. The Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits and serves as part of the neurologic examination. (revised per Amendment 04)

i: If the subject experiences visual disturbances during the course of the study, the subject will be referred to a specialist for a further ophthalmic examination, which should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields

j: Please refer to Section 9.4.7, which details prohibited and permitted medications in the study and associated timeframes.

k: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

l: Lymphocyte subsets will include but are not limited to the following cell surface marker assessments: CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [NK cells] and CD14 [macrophages]) and absolute lymphocytes. Regulatory T cells will also be measured. Viability staining may also be employed. Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a Complete Blood Count, with differentials, must also be performed along with assessment of AEs. (revised per Amendments 02 and 04)

m: Igs to be analyzed include IgG, IgA, and IgM.

n: An additional assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

o: Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops a TEAE that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

p: These assessments are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The order of assessments will be: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). At visits where the CDR or FAQ are conducted, the investigator will determine whether the informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

q: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images in MRI will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, 18, and 20. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be

**Footnotes for Table 7**

conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A volumetric MRI sequence will be collected in all subjects immediately following all safety MRI assessments. (revised per Amendment 01)

r: PET scanning will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks. A PET scan will only be performed at Visit 18 or ED if the subject has a valid Screening PET scan for the purposes of longitudinal analyses; subjects who were determined to be eligible for the study on the basis of an historical PET scan will not have a PET scan performed at Visit 18 or ED (revised per Amendment 02)

s: Site staff will contact the subject or the caregiver or informant the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the caregiver or informant, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

t: Two plasma PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visit 5, Visit 11, Visit 14, and Visit 16 and 4 to 8 hours postdose at Visit 7 and Visit 18 (or ED). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or ED) the PK blood sample should be collected shortly before or shortly after completing the LP. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected, followed by LP at approximately the same time as at previous visits. A second PK blood sample will be collected as close as possible to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

u: PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day. At Visits 5, 11, 14, and 16 the PD blood samples should be collected predose.

v: For subjects who consent to CSF sample collection: Postrandomization CSF sample collection is scheduled at Visit 7 (or later postrandomization timepoint) and Visit 18/ED. If a postrandomization CSF sample is collected later than Visit 7, time-matched plasma PK samples are also required (see Footnote t). All visits at which CSF samples are scheduled to be taken also include blood PK and PD assessments and so the subject will be dosed at the clinic on these days. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 [or later postrandomization timepoint] and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If the LP and the cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendments 01, 02, and 04)

w: Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

x: The first dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time as determined by the PI or Safety Physician for postdose medical observation. (revised per Amendment 02)

#### 9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 6 and Table 7 for the timings of the procedures and assessments to be performed during the Core Study. Screening assessments will be organized into 4 tiers (see Table 6, Section 9.5.2, and Figure 2. (revised per amendment 07)

See Section 9.5 for a full description of the procedures and assessments to be performed during this study.

Table 8 presents the number of blood and CSF samples, and the total volume of blood and CSF that will be collected throughout the Core Study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety. (revised per amendment 07)

**Table 8 Summary of Blood and CSF Sample Volumes**

| Assessment | Total number of collection time points | Number of time points × volume per collection (mL whole blood or CSF) | | Total volume (mL whole blood or CSF) |
|---|---|---|---|---|
| | | Screening and Baseline Periods | Treatment and Follow-up Periods | |
| **Blood** | | | | |
| Chemistry | 12 | 2 × 2 mL | 10 × 2 mL | 24 mL |
| Hematology | 20 | 2 × 5 mL | 18 × 5 mL | 100 mL |
| Lymphocyte subset analyses[a] | 20 | 2 × 4 mL | 18 × 4 mL | 80 mL |
| PBMC | 4 | 1 × 16 mL | 3 × 16 mL | 64 mL |
| IgA, IgM, IgG | 10 | 2 × 2 mL | 8 × 2 mL | 20 mL |
| PT, PTT for INR | 2 | 2 × 3 mL | None | 6 mL |
| Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxin) | 1 | 1 × 3 mL | None | 3 mL |
| Viral screen (Hepatitis B and C) | 1 | 1 × 4 mL | None | 4 mL |
| Viral characterization | 1 | 1 × 4 mL | None | 4 mL |
| Vitamin B12 | 1 | 1 × 2 mL | None | 2 mL |
| Serum pregnancy test | 1 | 1 × 2 mL | None | 2 mL |
| Tuberculosis (interferon-gamma release assays) | 1 | 1 × 3 mL | None | 3 mL |
| Sample for immune status | 8 | 1 × 4 mL | 7 × 4 mL | 32 mL |
| PD sample | 9 | 1 × 4 mL | 8 × 4 mL | 36 mL |
| PK analysis | 7 | 1 × 3 mL | 6 × 6 mL | 39 mL |
| Pharmacogenetic sample | 1 | 1 × 3 mL | None | 3 mL |
| All blood samples, total volume whole blood collected | | 80 mL | 342 mL | 422 mL |
| **CSF (For subjects who consent to CSF sample collection) (revised per Amendment 02)** | | | | |
| PD and PK samples | 3 | 1 × 12 mL | 2 × 12 mL | 36 mL |

CSF = cerebrospinal fluid, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetic, PT = prothrombin time, PTT = partial thromboplastin time.

a: Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials must also be performed. Therefore, for each unscheduled or repeat test, an additional 9 mL will be collected (5 mL for hematology and 4 mL for lymphocyte subset analyses)

(Table 8 revised per Amendment 04)

### 9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include vital signs, clinical laboratory assessments, physical examinations, ECG measurements, and reports of AEs. MRI will be used to detect vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage and is a standard evaluation to ensure subject safety. The C-SSRS has been endorsed by the FDA as a measure of potential suicidality (Guidance for Industry Suicidality).

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with elenbecestat, in addition to mitigating clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. Details are provided in Section 9.2.5.

### 9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

#### 9.5.4.1 Reporting of Serious Adverse Events

**All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.**

SAEs, regardless of causality assessment, must be collected up to 3 months after the last dose of study drug, ie, through to the final Follow-up Visit (Visit 20 for subjects who do not enter the Extension Phase or Follow-up Week 12 Visit for subjects who participate in the Extension Phase). (revised per Amendments 04, 05, 07, and 08) However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

**For urgent safety issues**, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

#### 9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must discontinue study treatment.

#### 9.5.4.3 Reporting of Events Associated with Special Situations

##### 9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

| | |
|---|---|
| Overdose | Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose |
| Misuse | Intentional and inappropriate use of study drug not in accordance with the protocol |
| Abuse | Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects |
| Medication error | Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject |

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

##### 9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2) should always be considered serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

#### 9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

#### 9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

#### 9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

### 9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue study drug or withdraw from the study at any time for any reason. All subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-up Visits will be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug in the Core Study (Visits W2, 19, W8, and Visit 20, respectively) or 4 and 12 weeks after the last dose of study drug in the Extension Phase (see Section 9.1.2.3). (revised per Amendments 04, 07, and 08) See Table 7 and Table 14 for full details of the assessments to be performed at these visits. (revised per Amendments 05 and 07) Subjects who discontinue study drug early (as opposed to subjects whose dosing with study drug is temporarily suspended under medical monitor guidance) will not be permitted to restart study drug.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and will provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who withdraw prematurely from the study will be withdrawn for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary

reason, the subject may indicate 1 or more secondary reason(s) for withdrawal from the study. Study disposition information will be collected on the Subject Disposition eCRF.

A subject removed from the study for any reason may not be replaced.

### 9.5.6 Abuse or Diversion of Study Drug

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF. (revised per Amendment 04)

### 9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

## 9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

### 9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

### 9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy assessments performed in this study.

## 9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance. (revised per Amendment 05)

### 9.7.1 Statistical and Analytical Plans

The statistical analyses of Core Study data are described in the following sections. Statistical analyses of Extension Phase data are provided in Appendix 6. (revised per Amendment 07)

Analyses will be performed based on treatment group, which will be defined in the statistical analysis plan (SAP). Additional analyses related to dose re-assignment will be performed for subjects who will be switched from elenbecestat 5 or 15 mg to elenbecestat 50 mg. Further details will be provided in the SAP, which will be finalized before database lock. (revised per Amendment 06)

#### 9.7.1.1 Study Endpoints

##### 9.7.1.1.1 PRIMARY ENDPOINT

- Safety and tolerability, which include incidence of TEAEs and SAEs, laboratory parameters, vital signs, and ECG parameters (revised per Amendment 05)

##### 9.7.1.1.2 SECONDARY ENDPOINTS

(revised per Amendments 02 and 05)

- % reduction of Aβ(1-x) and Aβ(1-42) in CSF relative to baseline after from 4 weeks and up to 18 months of treatment

- The population PK parameters of elenbecestat in CSF and plasma, including the effect of intrinsic and extrinsic factors (including NAT2 phenotype) (revised per Amendment 07)

#### 9.7.1.1.3 EXPLORATORY ENDPOINTS

(revised per Amendments 01, 02, 04, and 05)

Change from baseline in:

- CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) after at least 4 weeks and at 18 months of treatment
- CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment (revised per Amendment 06)
- Total hippocampal volume at 12 and 18 months of treatment as measured by vMRI
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months of treatment as measured by vMRI
- Amyloid PET standardized uptake value ratio (SUVR) composite at 18 months for brain amyloid levels as measured
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog14, CDR, MMSE, ISLT, CBB, and FAQ

### 9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose exploratory efficacy measurement. (revised per Amendment 05)
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat plasma concentration accompanied by a documented dosing history. (revised per Amendment 07)
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

### 9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening

Disposition eCRF. The number of randomized subjects enrolled at each site will be summarized by treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: The number (percent) of randomized and treated subjects who completed the study and who withdrew from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and withdrew from the study. The primary reasons for discontinuation from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

Completion of Study Treatment: The number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for discontinuation from the study drug are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, inadequate therapeutic response, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

#### 9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized by treatment group using descriptive statistics. Continuous demographic and baseline variables include age, MMSE and FAQ; categorical variables include sex, age group (≤65 years, age >65 years), race, ethnicity, *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal AD or mild to moderate AD). (revised per Amendment 01)

#### 9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014 or higher). (revised per Amendment 04) The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug

and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-up Period will also be recorded.

#### 9.7.1.6 Efficacy and Biomarker Analyses (revised per Amendment 05)

##### 9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

There is no primary efficacy endpoint. (revised per Amendment 05)

##### 9.7.1.6.2 SECONDARY EFFICACY ANALYSES

An mixed-effects model with repeated measures (MMRM) will be used to analyze the following secondary endpoint:

- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) from 4 weeks and up to 18 months. Data from early discontinuations will also be included. (revised per Amendment 05)

##### 9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

(revised per Amendments 01, 02, 04, and 05)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months. Data from early discontinuations will also be included. (revised per Amendment 04)
- Change from baseline in CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Change from baseline in plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- Change from baseline in CSF amyloid and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment (revised per Amendment 06)
- Change from baseline in total hippocampal atrophy at 12 and 18 months as measured by vMRI
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months as measured by vMRI
- Change from baseline in Amyloid PET SUVR composite at 18 months for brain amyloid levels

The following efficacy endpoints will be summarized using descriptive statistics:

- Change from baseline in the clinical assessments: ADAS-cog14, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months

The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

#### 9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

##### 9.7.1.7.1 PHARMACOKINETIC ANALYSES

The PK Analysis Set will be used for elenbecestat concentration listings and for summaries of elenbecestat concentrations in plasma and CSF by dose and day. Elenbecestat metabolite PK data may also be listed and summarized. (revised per Amendment 04)

A population PK approach will be used to characterize the plasma PK of elenbecestat. For this approach, plasma PK data from this study will be pooled with relevant data from Phase 1 studies. As appropriate, the effect of covariates on the PK of elenbecestat will be evaluated. The PK model will be parameterized for oral clearance (CL/F) and apparent volume of distribution (Vz/F) for elenbecestat. Derived exposure parameters such as steady state AUC and average concentration ($C_{avg}$) of elenbecestat and other derived parameters will be calculated from the model using the individual estimates parameterized for oral clearance and dosing history. (revised per Amendment 04)

##### 9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Pharmacodynamic, PGx, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate statistical analysis plan. Please also refer to Appendix 3.

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). The percentage change from baseline in CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months of treatment will be analyzed and presented graphically. (revised per Amendment 05) Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status. (revised per Amendment 04)

Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels, amyloid load on PET, vMRI, and elenbecestat dose, plasma, and CSF exposure will be initially explored graphically and any emergent relationship will be explored through population PK/PD modeling. The PK/PD relationship between plasma PK parameters with other biomarkers may also be explored using similar methods. (revised per Amendment 04)

The relationship between plasma and CSF exposure to elenbecestat and the clinical efficacy scales (eg, MMSE, CDR) will be explored graphically. Additionally, the relationship between plasma exposures of elenbecestat and select lymphocyte parameters will be explored graphically, and any emergent relationship will be explored using population-based modeling methods. (revised per Amendment 04)

Exposure-safety analyses may also be conducted.

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. The genomic DNA samples may also be stored and used as described in Section 9.7.1.7.2. Details of PGx testing may be provided and reported separately.

#### 9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements, and cognitive decline assessment such as CBB will be summarized by treatment group using descriptive statistics. (revised per Amendment 05)

##### 9.7.1.8.1 Extent of Exposure

The extent of exposure to study drug will be summarized as cumulative extent of exposure in 3-month intervals. The cumulative number and percent of subjects will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as continuous variable as well as categorical variable in 3-month intervals and the number and percent of subjects will be presented by treatment group.

#### 9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 17.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and preferred term. A subject will be counted only once within an SOC and preferred term, even if the subject experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and preferred term. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

Adverse events will be summarized by the following subgroups: *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal or mild to moderate AD). (revised per Amendment 01)

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

#### 9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the Treatment Period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

Lymphocyte subsets measured (including but not limited to CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages] and regulatory T cells) will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose.

Serum IgG, IgM, and IgA will be measured and summarized in the same manner as other laboratory parameters.

#### 9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

#### 9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to the end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF during the Treatment Period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 msec
- QTc interval >480 msec
- QTc interval >500 msec

Change from baseline in QTc interval:

- QTc interval increases from baseline >30 msec
- QTc interval increases from baseline >60 msec

#### 9.7.1.8.6 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include CBB (Section 9.7.1.6). (revised per Amendment 05)

### 9.7.2 Determination of Sample Size

A total of 15 subjects per dose group is deemed sufficient to derive adequate safety and PK/PD data to aid in the selection of appropriate doses and the design of the Phase 3 studies that may be planned subsequently. (revised per Amendment 05)

### 9.7.3 Interim Analysis

In order to make decisions about the remainder of the study as well as the full elenbecestat clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. Investigators, other clinical site staff, subjects, caregivers/informants, and study team will remain blinded to study treatment. (revised per Amendments 03 and 05)

An interim safety analysis will also be conducted when all subjects have completed 12 weeks of treatment (or discontinue study drug early). (revised per Amendments 01, 03, 04, and 05)

### 9.7.4 Other Statistical/Analytical Issues

**Stratification** (revised per Amendment 01)

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

### 9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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# 11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

## 11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

## 11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

## 11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

## 11.4 Recording of Data

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document, except when a section of the eCRF itself is used as the source document. Any correction to entries made on the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each eCRF. The investigator will report the eCRFs to the sponsor and retain a copy of the eCRFs.

## 11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents.

## 11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

## 11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

## 11.8 Handling of Study Drug

All study drugs will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

## 11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

## 11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or CTA executed between the institution/investigator and the sponsor/CRO.

## 11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

## 11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

# 12 APPENDICES

## Appendix 1 Sponsor's Grading for Laboratory Values

(revised per Amendment 01)

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **BLOOD/BONE MARROW** | | | | |
| Hemoglobin (conversion from g/dL×0.6206) | **Female** (ULN = 15.9 g/dL)<br><11.1 – 10.0 g/dL<br><111 – 100 g/L<br><6.9 – 6.2 mmol/L<br>**Male** (ULN = 17.7 g/dL)<br><12.6 – 10.0 g/dL<br><126 – 100 g/L<br><7.8 – 6.2 mmol/L | <10.0 – 8.0 g/dL<br><100 – 80 g/L<br><6.2 – 4.9 mmol/L | <8.0 g/dL<br><80 g/L<br><4.9 mmol/L;<br>transfusion indicated | life-threatening consequences; urgent intervention indicated |
| Leukocytes (total white blood cell) | <3.40 – 3.0×$10^9$/L<br><3.40 $10^3$/uL – 3000/$mm^3$<br>(ULN = 10.80 $10^3$/μL) | <3.0 – 2.0×$10^9$/L<br><3000 – 2000/$mm^3$ | <2.0 – 1.0×$10^9$/L<br><2000 – 1000/$mm^3$ | <1.0×$10^9$/L<br><1000/$mm^3$ |
| Lymphocytes | not applicable | <700 – 500/$mm^3$<br><0.7 – 0.5×$10^9$/L | <500 – 200/$mm^3$<br><0.5 – 0.2×$10^9$/L | <200/$mm^3$<br><0.2×$10^9$/L |
| Neutrophils | not applicable | <1.4 – 1.0×$10^9$/L<br><1400 – 1000/$mm^3$ | <1.0 – 0.5×$10^9$/L<br><1000 – 500/$mm^3$ | <0.5×$10^9$/L<br><500/$mm^3$ |
| Platelets | <155 – 75.0×$10^9$/L<br><155 $10^3$/uL – 75,000/$mm^3$<br>(ULN = 379 $10^3$/μL) | <75.0 – 50.0×$10^9$/L<br><75,000 – 50,000/$mm^3$ | <50.0 – 25.0×$10^9$/L<br><50,000 – 25,000/$mm^3$ | <25.0×$10^9$/L<br><25,000/$mm^3$ |
| **METABOLIC/LABORATORY** | | | | |
| Albumin, serum- low (hypoalbuminemia) | **2 - 59 years** (ULN = 5.5 g/dL)<br><3.5 – 3 g/dL<br><35 – 30 g/L<br>**59 - 69 years** (LLN-ULN)<br><3.6 g/dL – 3 g/dL<br>**69 - 79 years** (LLN-ULN)<br><3.5 g/dL – 3 g/dL<br>**79 - 89 years** (LLN-ULN)<br><3.5 g/dL – 3 g/dL | <3 – 2 g/dL<br><30 – 20 g/L | <2 g/dL<br><20 g/L | life-threatening consequences; urgent intervention indicated |
| Alkaline phosphatase | **Female:**<br>**18 - 19 years**<br>>101 – 3.0×101<br>**19 - 61 years**<br>ULN=107<br>**61 - 71 years**<br>ULN=112<br>**71 - 150 years**<br>ULN=108<br>**Male**<br>**18 - 19 years**<br>>127 – 3.0×127<br>**19 - 61 years**<br>ULN=102<br>**61 - 71 years**<br>ULN=103<br>**71 - 150 years**<br>ULN=105 | >3.0 – 5.0×ULN<br>See previous column for ULN values | >5.0 – 20.0×ULN<br>See previous column for ULN values | >20.0×ULN<br>See previous column for ULN values |
| Alanine aminotransferase | **Female:**<br>>32 – 3.0×32 | **Female:**<br>>3.0 – 5.0×32 | **Female:**<br>>5.0 – 20.0×32 | **Female:**<br>>20.0×32 |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| | **Male:**<br>>44 – 3.0 x 44 | **Male**<br>>3.0 – 5.0×44 | **Male:**<br>>5.0 – 20.0×44 | **Male:**<br>>20.0×44 |
| Aspartate aminotransferase | >40 – 3.0×40 | >3.0 – 5.0×40 | >5.0 – 20.0×40 | >20.0×40 |
| Bilirubin (hyperbilirubinemia) | >1.2 – 1.5×1.2 | >1.5 – 3.0×1.2 | >3.0 – 10.0×1.2 | >10.0×1.2 |
| Calcium, serum-low (hypocalcemia) (conversion to mmol×0.25) | <8.5 – 8.0 mg/dL<br><2.13 – 2.0 mmol/L | <8.0 – 7.0 mg/dL<br><2.0 – 1.75 mmol/L | <7.0 – 6.0 mg/dL<br><1.75 – 1.5 mmol/L | <6.0 mg/dL<br><1.5 mmol/L |
| Calcium, serum-high (hypercalcemia) | >10.6 – 11.5 mg/dL<br>>2.65 – 2.9 mmol/L | >11.5 – 12.5 mg/dL<br>>2.9 – 3.1 mmol/L | >12.5 – 13.5 mg/dL<br>>3.1 – 3.4 mmol/L | >13.5 mg/dL<br>>3.4 mmol/L |
| Cholesterol, serum-high (hypercholesterolemia) (conversion to mmol/L ×0.02586) | **0 - 19 years**<br>>169 – 300 mg/dL<br>>4.37 – 7.75 mmol/L<br>**19 - 150 years**<br>>199 – 300 mg/dL<br>>5.15 – 7.75 mmol/L | >300 – 400 mg/dL<br>>7.75 – 10.34 mmol/L | >400 – 500 mg/dL<br>>10.34 – 12.92 mmol/L | >500 mg/dL<br>>12.92 mmol/L |
| Creatinine | **Female**<br>>1.00 mg/dL – 1.5×1.00<br>**Male**<br>>1.27 mg/dL – 1.5×1.27 | **Female**<br>>1.5 – 3.0×1.00<br>**Male**<br>>1.5 mg/dL – 3.0×1.27 | **Female**<br>>3.0 – 6.0×1.00<br>**Male**<br>>3.0 mg/dL – 6.0 ×1.27 | **Female**<br>>6.0×1.00<br>**Male**<br>>6.0×1.27 |
| Gamma glutamyl transpeptidase | **Female**<br>>60 IU/L – 3.0×60<br>**Male**<br>>65 IU/L – 3.0×65 | **Female**<br>>3.0 – 5.0×60<br>**Male**<br>>3.0 – 5.0×65 | **Female**<br>>5.0 – 20.0×60<br>**Male**<br>>5.0 – 20.0×65 | **Female**<br>>20.0×60<br>**Male**<br>>20.0×65 |
| Glucose, serum-high (hyperglycemia) (conversion to mmol/L ×0.0555) | **Fasting glucose value**<br>>99 – 160 mg/dL<br>>5.5 – 8.9 mmol/L | **Fasting glucose value**<br>>160 – 250 mg/dL<br>>8.9 – 13.9 mmol/L | >250 – 500 mg/dL;<br>>13.9 – 27.8 mmol/L;<br>hospitalization indicated | >500 mg/dL;<br>>27.8 mmol/L;<br>life-threatening consequences |
| Glucose, serum-low (hypoglycemia) | <65 – 55 mg/dL<br><3.6 – 3.0 mmol/L | <55 – 40 mg/dL<br><3.0 – 2.2 mmol/L | <40 – 30 mg/dL<br><2.2 – 1.7 mmol/L | <30 mg/dL<br><1.7 mmol/L<br>life-threatening consequences;<br>seizures |
| Phosphate, serum-low (hypophosphatemia) (conversion to mmol/L ×0.323) | not applicable | <2.5 – 2.0 mg/dL<br><0.8 – 0.6 mmol/L | <2.0 – 1.0 mg/dL<br><0.6 – 0.3 mmol/L | <1.0 mg/dL<br><0.3 mmol/L<br>life-threatening consequences |
| Potassium, serum-high (hyperkalemia) | not applicable | >5.5 – 6.0 mmol/L | >6.0 – 7.0 mmol/L<br>hospitalization indicated | >7.0 mmol/L<br>life-threatening consequences |
| Potassium, serum-low (hypokalemia) | <3.5 mEq/L – 3.0 mmol/L | <LLN – 3.0 mmol/L;<br>symptomatic; intervention indicated | <3.0 – 2.5 mmol/L<br>hospitalization indicated | <2.5 mmol/L<br>life-threatening consequences |
| Sodium, serum-high (hypernatremia) | >144 mEq/L – 150 mmol/L | >150 – 155 mmol/L | >155 – 160 mmol/L<br>hospitalization indicated | >160 mmol/L<br>life-threatening consequences |
| Sodium, serum-low (hyponatremia) | <134 mEq/L – 130 mmol/L | Not applicable | <130 – 120 mmol/L | <120 mmol/L<br>life-threatening consequences |
| Triglyceride, serum-high (hypertriglyceridemia) | 150 – 300 mg/dL<br>1.71 – 3.42 mmol/L | >300 – 500 mg/dL<br>>3.42 – 5.7 mmol/L | >500 – 1000 mg/dL<br>>5.7 – 11.4 mmol/L | >1000 mg/dL<br>>11.4 mmol/L<br>life-threatening consequences |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Uric acid, serum-high (hyperuricemia) | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | Not applicable | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | >10 mg/dL<br>>0.59 mmol/L<br>life-threatening consequences |

LLN = lower limit of normal, ULN = upper limit of normal.

# Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1 through Listing 5. Medications permitted with restrictions are listed in Listing 6 through Listing 8. (revised per Amendment 04) **These may not be all-inclusive listings.** Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-202 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 8 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

## Prohibited Prior/Concomitant Medications

### Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Prohibited from 14 days (or 5 half-lives, whichever is longer) before Randomization until after the last treatment visit** | | |
| **Anti-arrhythmic/ abnormal heart rhythm** | | |
| Amiodarone | Cordarone; Pacerone | Incidence in females greater than males, Torsades de Pointes risk regarded as low |
| Disopyramide | Norpace | Incidence in females greater than males |
| Dofetillide | Tikosyn | |
| Ibutilide | Corvert | Incidence in females greater than males |
| Procainamide | Pronestyl; Procan | |
| Quinidine | Cardioquin; Quinaglute | Incidence in females greater than males |
| Sotalol | Betapace | Incidence in females greater than males |
| **Antihistamine/ allergic rhinitis** | | |
| Astemizole | Hismanal | No longer available in United States |
| Terfenadine | Seldane | No longer available in United States |
| **Anti-anginal/ heart pain** | | |
| Bepridil | Vascor | Incidence in females greater than males |
| **Antibiotic/ bacterial infection** | | |
| Clarithromycin | Biaxin | |
| Moxifloxacin | Avelox | |
| Sparfloxadin | Zagam | |
| **Listing 1 continued** | | |
| **Antimalarial/ malaria infection** | | |
| Chloroquine | Aralen | |
| Halofantrine | Halfan | Incidence in females greater than males |
| **Antipsychotic/ anti-emetic/ schizophrenia/ nausea** | | |
| Chloropromazine | Thorazine | |
| **Gastrointestinal stimulant/ heartburn** | | |
| Cisapride | Propulsid | |

## Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Antinausea/ nausea** | | |
| Domperidone | Motillum | Not available in the United States |
| **Sedative; antinausea/ anesthesia adjunct, nausea** | | |
| Droperidol | Inapsine | |
| **Antibiotic; gastrointestinal stimulant/ bacterial infection; increase gastrointestinal motility** | | |
| Erythromycin | Erythrocin; E.E.S. | Incidence in females greater than males |
| **Antipsychotic/ schizophrenia** | | |
| Haloperidol | Haldol | When given intravenously or at higher than recommended doses, risk of sudden death, QT prolongation, and torsades increases |
| Mesoridazine | Serentil | |
| Thioridazine | Mellaril | |
| **Opiate agonist/ pain control, narcotic dependence** | | |
| Levomethadyl | Orlaam | |
| Methadone | Methadose; Dolophine | Incidence in females greater than males |
| **Anti-infective/ pneumocystis pneumonia** | | |
| Pentamidine | Pentam; NebuPent | Incidence in females greater than males |
| **Antipsychotic/ Tourette's tics** | | |
| Pimozide | Orap | Incidence in females greater than males |
| **Antilipemic/ hypercholesterolemia** | | |
| Probucol | Lorelco | No longer available in United States |
| **Anticancer** | | |
| Arsenic trioxide | Trisenox | Used for leukemia |
| Vandetanib | Zactima | Used for thyroid cancer |

Note: This list is not exhaustive.

QTc = Corrected QT interval.

## Listing 2 Prohibited Medications Within 5 Half-lives or 60 days, Whichever is Longer, Before Randomization and Until after the Last Treatment Visit

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Systemic Immunosuppressants[a,b] and Immunomodulatory therapy** | |
| Azathioprine | Azasan, Imur |
| Ciclosporine | Gengraf, Neoral |
| Dexamethasone | Decadron, Dexasone, Diodex, Hexadrol, Maxidex |
| Fingolimod | Gilenya |
| Methotrexate | Trexall |
| Methylprednisolone | Medrol, Meprolone |
| Mycophenolate | CellCept, Myfortic |
| Prednisolone | Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS |

Note: This list is not exhaustive.

a: Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

b: During the Treatment Period of the study, short term (not more than 14 days) use of steroids up to the equivalent of prednisolone 40 mg QD is permitted after discussion with the medical monitor. Dosing with study drug should be suspended from the time steroid treatment is started. Complete blood count and lymphocyte subsets (for Core Study and the first 12 months of Extension Phase only) should be determined before starting steroid treatment and continue to be monitored weekly. (revised per Amendment 08) Study drug may be resumed after discussion with the medical monitor when the following conditions are met: (1) treatment with steroids has been completed for at least 1 week; (2) absolute lymphocytes not <LLN; (3) no lymphocyte subsets are below the discontinuation threshold (for Core Study only); (4) the investigator considers that the medical condition which required treatment with steroids has improved or resolved. Weekly testing of lymphocyte subset counts (for Core Study only) and CBC with differentials is required for 4 weeks following resumption of study drug administration. (revised per Amendment 04)

## Listing 3 Prohibited Medications Within 6 Months Before Randomization

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Immunoglobulin therapy** | |
| Adalimumab | Humira |
| Bevacizumab | Avastin |
| Efalizumab | Raptiva |
| Etanercept | Enbrel |
| Immune globulin IV, IVIG, IGIV | Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S |
| Infliximab | Remicade |
| Omalizumab | Xolair |
| Ranibizumab | Lucentis |
| Other monoclonal antibodies not listed here | |

Note: This list is not exhaustive.

## Listing 4 Prohibited Live Vaccines Within 3 Months Before Randomization Until after the Last Treatment Visit (this does not apply to non-live/inactivated vaccines)

| **Bacterial vaccines** | **Viral vaccines** |
|---|---|
| Bacillus Calmette-Guérin vaccine against tuberculosis | Measles vaccination |
| Cholera vaccination (oral) | Rubella vaccination |
| | Oral polio vaccination (Sabin) |
| | Yellow fever vaccination |
| | Varicella (chickenpox) vaccination |
| | Rotavirus vaccination |
| | Japanese encephalitis vaccination |
| | Live attenuated influenza vaccine (FluMist, Fluenz) |
| Typhoid vaccination (oral) | Mumps vaccination |

Note: This list is not exhaustive

## Listing 5 Strong CYP3A4 Inhibitors Prohibited Within 5 Half-Lives or 14 Days (Whichever Is Longer) Before Randomization Until After the Last Treatment Visit

| Generic name | Brand name(s) |
|---|---|
| boceprevir | Victrelis |
| clarithromycin | Clarithromycin, clarithromycin extended release, Prevpac |
| cobicistat | Tybost, Stribild, |
| conivaptan | Vaprisol |
| danoprevir | |
| elvitegravir | Vitekta, Stribild |
| indinavir | Crixivan |
| itraconazole | Sporanoz, Onmel |
| ketoconazole | Xolegel, Nizoral, Ketodan |
| lopinavir | Kaletra |
| nefazodone | Serzone |
| nelfinavir | Viracept |
| posaconazole | Noxafil |
| ritonavir | Norvir, Kaletra |
| saquinavir | Invirase, Fortovase |
| telaprevir | Incivek |
| telithromycin | Ketek |
| tipranavir | Aptivus |
| troleandomycin | Triocetin |
| voriconazole | Vfend, Voriconazole |

Note: This list is not exhaustive

## Permitted Prior/Concomitant Medications

### Listing 6 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Baseline Cognitive Assessments at Visit 2 and Remain on the Same Stable Dose from Baseline to Final Follow-Up Visit

| **Generic name** | **Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™)** |
|---|---|
| **Cognitive Enhancers** | |
| Donepezil | Aricept |
| Galantamine | Reminyl |
| Memantine | Namenda |
| Rivastigmine | Exelon |

Note: This list is not exhaustive.

## Listing 7 Permitted Medications Used on PRN Basis Which are Not to be Used Within 72 Hours before Cognitive Testing

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Opiates** | |
| Morphine | Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol |
| **Opiate Agonists** | |
| Codeine | Codeine |
| Fentanyl | Actiq, Duragesic, Fentora, Onsolis, Sublimaze |
| Meperidine | Demerol, Meperitab |
| Oxycodone | Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol |
| Other opioids or opioid agonists which are used on PRN basis | |
| **Benzodiazepines and sedatives** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Amitriptyline | (various) |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Dothiepin | (various) |
| Estazolam | ProSom |
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |
| Lorazepam | Ativan |
| Midazolam | Versed |
| Olanzapine | Zyprexa |
| Promethazine | Phenergan; others |
| Ramelteon | Rozerem |
| Risperidone | Risperdal |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zolpidem | Ambien; others |
| Zopiclone | (various) |
| Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives | |

Note: This list is not exhaustive

PRN = Pro re nata

## Listing 8 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| If to be used on a PRN basis see Listing 7. If to be used chronically, subjects must be on a stable dose for ≥4 weeks before Baseline. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks. | |
| **Antidepressants** | |
| Amitriptyline hydrochloride | Elavil |
| Amoxapine | Amoxapine |
| Bupropion | Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin |
| Citalopram | Celexa |
| Clomipramine hydrochloride | Anafranil |
| Desipramine hydrochloride | Norpramin |
| Desvenlafaxine | Pristiq |
| Doxepin hydrochloride | Prudoxin, Silenor, Sinequan, Zonalon |
| Duloxetine | Cymbalta |
| Escitalopram | Lexapro |
| Fluoxetine | Prozac, Sarafem, Selfemra |
| Fluvoxamine | Luvox |
| Imipramine hydrochloride | Tofranil |
| Isocarboxazid | Marplan |
| Maprotiline hydrochloride | Ludiomil |
| Mirtazapine | Remeron Soltab |
| Nortriptyline hydrochloride | Aventyl, Pamelor |
| Paroxetine | Paxil, Pexeva |
| Phenelzine | Nardil |
| Protriptyline hydrochloride | Vivactil |
| Rasagiline | Azilect |
| Selegiline | EMSAM |
| Sertraline | Sertaraline, Zoloft |
| Tranylcypromine | Parnate |
| Trazodone hydrochloride | Desyrel, Oleptro |
| Trimipramine maleate | Surmontil |
| Venlafaxine hydrochloride | Effexor |

## Listing 8 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Mood Stabilizers (Listing 8 continued)** | |
| Carbamazepine | Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR |
| Lamotrigine | Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR |
| Valproic acid | Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate |
| **Antipsychotics** | |
| Acetophenazine | Tindal |
| Aripiprazole | Abilify |
| Asenapine | Saphris |
| Olanzapine | Zyprexa |
| Chlorpromazine | Thorazine |
| Haloperidol | Haloperidol, Haldol |
| Clozapine | Clozaril, Fazaclo |
| Fluphenazine | Prolixin |
| L-Methylfolate | Deplin, L-Methylfolate Calcium |
| Loxapine | Loxitane |
| Mesoridazine | Serentil |
| Perphenazine | Trilafon |
| Quetiapine | Seroquel |
| Risperidone | Risperdal |
| Thioridazine | Mellaril |
| Thiothixene | Navane |
| Trifluoperazine | Stelazine |
| **Benzodiazepines** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Estazolam | ProSom |
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |
| Lorazepam | Ativan |

## Listing 8 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| Midazolam | Versed |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zopiclone | Imovane, Zimovane |
| Zopidem | Ambien, Ambien CR, Intermezzo, Stilnox, Stilnoct, Sublinox, Hypnogen, Zolsana |

Note: This list is not exhaustive.

PRN = Pro re nata

# Appendix 3 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for pharmacodynamic (PD), pharmacogenomic (PGx), and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events (AEs) related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

## Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

## Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health

authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] E15 guidelines) in order to maintain subject privacy.

### Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

### Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject indentification [ID]) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- Contract research organizations (CROs) retained by the sponsor
- Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs) that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

# Appendix 4 AEs Indicating Signals of Possible Drug Abuse Potential

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| 1 | **Euphoric mood** | Euphoric mood |
| | | Euphoria |
| | | Euphoric |
| | | Exaggerated well-being |
| | | Excitement excessive |
| | | Feeling high |
| | | Felt high |
| | | High |
| | | High feeling |
| | | Laughter |
| 2 | **Elevated mood** | Elevated mood |
| | | Mood elevated |
| | | Elation |
| 3 | **Feeling abnormal** | Feeling abnormal |
| | | Cotton wool in head |
| | | Feeling dazed |
| | | Feeling floating |
| | | Feeling strange |
| | | Feeling weightless |
| | | Felt like a zombie |
| | | Floating feeling |
| | | Foggy feeling in head |
| | | Funny episode |
| | | Fuzzy |
| | | Fuzzy head |
| | | Muzzy head |
| | | Spaced out |
| | | Unstable feeling |
| | | Weird feeling |
| | | Spacey |
| 4 | **Feeling drunk** | Feeling drunk |
| | | Drunkenness feeling of |
| | | Drunk-like effect |
| | | Intoxicated |
| | | Stoned |
| | | Drugged |
| 5 | **Feeling of relaxation** | Feeling of relaxation |
| | | Feeling relaxed |
| | | Relaxation |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Relaxed |
| | | Increased well-being |
| | | Excessive happiness |
| **6** | **Thinking abnormal** | Thinking abnormal |
| | | Abnormal thinking |
| | | Thinking irrational |
| | | Thinking disturbance |
| | | Thought blocking |
| | | Wandering thoughts |
| **7** | **Hallucination** | Hallucination |
| | | Illusions |
| | | Flashbacks |
| | | Floating |
| | | Rush |
| | | Feeling addicted |
| **8** | **Inappropriate affect** | Elation inappropriate |
| | | Exhilaration inappropriate |
| | | Feeling happy inappropriately |
| | | Inappropriate affect |
| | | Inappropriate elation |
| | | Inappropriate laughter |
| | | Inappropriate mood elevation |
| **9** | **Mood disorders and disturbances** | Mental disturbance |
| | | Depersonalisation |
| | | Psychomotor stimulation |
| | | Mood disorders |
| | | Emotional and mood disturbances |
| | | Delirium |
| | | Delirious |
| | | Mood altered |
| | | Mood alterations |
| | | Mood instability |
| | | Mood swings |
| | | Emotional lability |
| | | Emotional disorder |
| | | Emotional distress |
| | | Personality disorder |
| | | Impatience |
| | | Abnormal behavior |
| | | Delusional disorder |
| | | Irritability |
| **10** | **Drug tolerance** | Drug tolerance |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Habituation |
| | | Drug withdrawal syndrome |
| | | Substance-related disorders |
| **11** | **Psychosis** | Psychosis |
| | | Psychotic episode or disorder |
| **12** | **Dissociative State** | Dissociation |
| | | Disconnected |
| | | Derealisation |
| | | Depersonalisation |
| | | Detached |
| | | Sensation of distance from one's environment |
| | | Loss of a sense of personal identity |

# Appendix 5 Eisai Lymphocyte Subset Criteria for Study E2609-G000-202: Justification for a Population-Adjusted Approach

**Introduction:**

The Eisai clinical study, E2609-G000-202, requires the analysis of absolute numbers of various functional subsets of circulating lymphocytes. These are distinguished by identification of various complementary differentiation (CD) markers on the cell surface using fluorescent-labeled antibody reagents and flow cytometry. Current enumeration of certain lymphocyte subsets form part of the immunologically based eligibility criteria for study enrollment, as well as being monitored for safety for enrolled and treatment randomized subjects. The Trucount™ M (Becton, Dickinson and Company [BD], BD Biosciences, San Jose, CA) antibody reagents used for the lymphocyte subset eligibility criteria, provides readouts for both absolute (BD Trucount tubes) and percentage of lymphocyte subsets, and includes the following CD markers: CD3 (T cells), CD4 (T helper cells), CD8 (cytotoxic T cells), CD16/56 (natural killer cells), CD14 (macrophages), and CD19 (B cells).

Trucount lymphocyte subset reference ranges provided by the reagent manufacturer (BD) for both absolute and percentages were established for clinical use as an in vitro diagnostic using standardized reference interval methodology. These lower limits of normal (LLN) for the various lymphocyte subsets are currently being used by the central laboratory for Eisai Study E2609-G000-202 to determine eligibility of screened subjects and as part of safety assessments during post-randomization visits. The eligibility criterion excludes subjects with absolute counts of T and B cell markers (CD4, CD8, and CD19 respectively) less than the reference range LLN at Screening or Baseline.

**Need to assign age appropriate reference ranges:**

Reference ranges established by the vendor according to working group guidance (3) may not be representative of different subgroup analyses (eg, ancestry, disease state, age, gender, etc.), and therefore interval adjustment may be required depending on the subpopulation of interest. The working group guidance for reference intervals (Clinical and Laboratory Standards Institute's, 2010(4)) recommends examining data to determine if >10% of subjects are outliers (ie, more than 10% <LLN), and if so, to initiate development of subgroup-appropriate intervals by analyzing data from the literature or internal studies representing the reference population [a minimum of 120 observations recommended by the guidance.(3)]

Data from the ongoing Study E2609-G000-202 has been examined and greater than 10% of the study population screening samples fall below the manufacturer recommended LLN for the key lymphocyte subsets. The population for Study E2609-G000-202 are patients aged 50 to 85 years old inclusive with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) or with mild to moderate dementia due to AD. Lymphocyte subset data from a

data cut of 93 screened subjects was analyzed and showed that both CD8 and CD4 had greater than 10% of the subjects with results <LLN (26.9%, <220 cells/mm$^3$ and 13%, <404 cells/mm$^3$, respectively); CD19 had approximately 10% of the subjects with results <LLN (9.7%, <80 cells/mm$^3$).

To further determine if the outlier data observations from the ongoing Study E2609-G000-202 were associated with disease status or age, lymphocyte subset data from additional Eisai studies that included healthy elderly subjects or patients diagnosed with MCI or mild/moderate AD were examined. The individuals from all 3 studies included the same 50-to 85-year-old age range as the current E2609-G000-202 study. The studies evaluated include: (1) Study E2609-A001-002 treatment study (n=50 healthy elderly); (2) Lymphocyte subset pilot study in healthy elderly [n=30]; and (3) Lymphocyte subset pilot study in AD/MCI [n=31]. Screening or baseline sample from all 4 studies had >10% of the CD8 absolute counts below reference LLN, 2 out of 4 had >10% of the CD19 absolute counts below reference LLN and 1 out of 4 had >10% of the CD4 absolute counts out of reference LLN [Table 10, Table 11, and Table 12]. The data suggests that the reference values of LLN for CD4, CD8, and CD19 subsets are not a disease-associated observation but are related to the age of the study population being evaluated.

In addition to the Eisai study data, age related decline in lymphocyte subsets has been described in the literature Yan et al.(1)(2) Analysis was performed using flow cytometry on peripheral blood leukocytes using healthy subjects across the 3rd and 10th decades of life. The results from the Yan study (n=80; 37 males, 43 females) demonstrated that with advancing age there was a significant decline in the percentage of lymphocytes, specifically naive T cells [CD3 $P$=0.03], cytotoxic T cells [CD8 $P$=0.08] and activated B cells [CD20/CD69 $P$=0.03] with certain subsets demonstrating even greater decline in males.(1) The age associated changes in immune capabilities, termed “immunosenescence”, which include degenerative changes in the lymph nodes, effects on lymphocyte subsets and changes in adaptive immunity may underlie the increased risk of infection and cancer and decreased immune function in the elderly. This, along with the data from the four Eisai studies described earlier, support the readjustment of the LLNs for the CD reference ranges used for eligibility in Study E2609-G000-202 such that they are better suited to the older patient population enrolling in this study which is thought to be representative of the wider patient population.

**Determining the new LLN criteria:**

The recommended method for establishing reference intervals is the nonparametric approach where the underlying distribution of the data does not matter. The values received from the data (a minimum of 120 observations representing the subgroup population of interest is recommended) are rank ordered and can be used to evaluate the comparative reference interval.(3)

When data from the 4 Eisai studies are put in rank order (see Table 10, Table 11, and Table 12), and a 10% cut value is applied to each of the 3 CD markers of interest the following age-adjusted LLN values are generated:

**Table 9 Summary of CD4, CD8, and CD19 LLNs and Age-Adjusted LLNs**

| Lymphocyte Subset | Current LLN | Age-adjusted LLN |
|---|---|---|
| CD4 absolute count | 404 cells/$mm^3$ | 396 cells/$mm^3$ |
| CD8 absolute count | 220 cells/$mm^3$ | 157 cells/$mm^3$ |
| CD19 absolute count | 80 cells/$mm^3$ | 74 cells/$mm^3$ |

**Table 10 Summary of CD Counts (Parameter: CD19)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 30 | 203 |
| Mean | 213.47 | 198.49 | 159.20 | 172.77 | 192.57 |
| Median | 189.66 | 163.00 | 118.50 | 159.50 | 164.86 |
| 5th percentile | 84.81 | 59.00 | 38.00 | 69.00 | 59.00 |
| 10th percentile | 102.26 | 81.00 | 42.00 | 70.50 | 74.00 |
| 25th percentile | 139.66 | 104.00 | 75.00 | 100.00 | 104.58 |
| 75th percentile | 261.51 | 225.00 | 225.00 | 246.00 | 246.00 |
| 95th percentile | 376.67 | 443.00 | 424.00 | 384.00 | 402.00 |
| Range | 66.19, 593.48 | 17.00, 1066.00 | 37.00, 455.00 | 39.00, 415.00 | 17.00, 1066.00 |

**Table 11 Summary of CD Counts (Parameter: CD8)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 31 | 204 |
| Mean | 362.72 | 352.18 | 324.63 | 427.74 | 362.20 |
| Median | 364.74 | 330.00 | 344.00 | 315.00 | 336.39 |
| 5th percentile | 115.02 | 138.00 | 86.00 | 100.00 | 115.02 |
| 10th percentile | 170.24 | 151.00 | 159.50 | 153.00 | 157.00 |
| 25th percentile | 253.37 | 213.00 | 204.00 | 217.00 | 230.00 |
| 75th percentile | 465.52 | 425.00 | 405.00 | 494.00 | 438.00 |
| 95th percentile | 614.57 | 716.00 | 557.00 | 988.00 | 702.00 |

**Table 11 Summary of CD Counts (Parameter: CD8)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| Range | 98.45, 702.50 | 37.00, 803.00 | 61.00, 702.00 | 54.00, 2255.00 | 37.00, 2255.00 |

**Table 12 Summary of CD Counts (Parameter: CD4)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 31 | 204 |
| Mean | 846.15 | 839.58 | 789.27 | 804.52 | 828.46 |
| Median | 836.94 | 805.00 | 777.50 | 771.00 | 791.50 |
| 5th percentile | 388.44 | 337.00 | 395.00 | 351.00 | 344.00 |
| 10th percentile | 479.55 | 361.00 | 490.00 | 427.00 | 396.00 |
| 25th percentile | 639.54 | 620.00 | 661.00 | 669.00 | 633.77 |
| 75th percentile | 1031.49 | 1078.00 | 924.00 | 1014.00 | 1039.50 |
| 95th percentile | 1315.55 | 1404.00 | 1124.00 | 1327.00 | 1347.00 |
| Range | 274.90, 1643.55 | 197.00, 1481.00 | 248.00, 1720.00 | 143.00, 1336.00 | 143.00, 1720.00 |

References:

1. Yan et al., Immunity and Ageing 2010 v. 7:4; The effect of ageing on human lymphocyte subsets: comparison of males and females.
2. Wikby et al., Biogerontology 2008 vol 9: 299; The immune risk profile is associated with age and gender: findings from three Swedish population studies of individuals 20-100 years of age.
3. Horowitz eJIFCC 2008 vol. 19 (2) Reference intervals: practical aspects).
4. Horowitz et al., CLSI Vol 28 no. 30 Clinical and Laboratory Standards Institute's (CLSI) newly revised document Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition (C28-A3), published in November 2010 EP28-AC3

# Appendix 6 Extension Phase

(revised per Amendments 07 and 08)

**PRIMARY OBJECTIVE**

- To assess the long-term safety and tolerability of daily dosing with elenbecestat 50 mg in mild cognitive impairment (MCI)/Prodromal subjects and in subjects with mild to moderate dementia due to Alzheimer's disease (AD)

**SECONDARY OBJECTIVES**

- To explore the long-term effects of elenbecestat on clinical status by assessment of:
    a. The Mini-Mental State Examination (MMSE)
    b. The Functional Assessment Questionnaire (FAQ; also known as the Functional Activities Questionnaire)
- To explore the long-term effects of elenbecestat on:
    a. Volumetric magnetic resonance imaging (vMRI) including, but not limited to, total hippocampal volume, left and right hippocampal volume, whole brain volume, and total ventricular volume at 24 and 48 months of treatment in the Extension Phase.
    b. Plasma amyloid at 12, 24, 36, and 48 months of treatment in the Extension Phase

**ELIGIBILITY CRITERIA**

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

Inclusion:

1. Subjects who complete the 18-month treatment and the 12-week Follow-up Period (Visit 20) in the Core Study and whose Visit 20 falls within a 4-week window from the start of the Extension Phase (Visit 21). Permission must be obtained from the medical monitor if Visit 21 is to occur more than 4 weeks from Visit 20.
2. Subjects must continue to have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the Extension Phase.

Exclusion:

1. Subjects who discontinue study drug prematurely during the Core Study are not eligible to participate in the Extension Phase.

2. Subjects with any active infection within 4 weeks of Visit 21
3. Subjects with absolute lymphocyte count below the Lower Limit of Normal (LLN) within 10 days of Visit 21
4. Subjects who develop the following conditions from the time of screening for the Core Study to the start of the Extension Phase:
    a. Hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7. Subjects with Gilbert's syndrome need not be excluded on the basis of an elevated bilirubin, provided that they have no other signs or symptoms suggestive of hepatic impairment
    b. Any contraindications to magnetic resonance imaging (MRI) scanning, including cardiac pacemaker/defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners)
    c. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
    d. Immunoglobulin (Ig) deficiency or other immunodeficiency disorders
    e. Chronic viral hepatitis
    f. Tuberculosis (TB)
    g. Ophthalmic shingles
    h. Ocular herpes simplex virus (HSV) infection
    i. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
        - Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded
        - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded
        - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted)
    j. Malignant neoplasms (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject from the Extension Phase).
5. Subjects with prolonged QTcF interval at Visit 20 or Visit 21. Subjects with a single 12-lead ECG QTcF >450 msec should have 2 additional ECGs performed at least

1 minute apart and the mean QTcF from the triplicate ECGs should be calculated. Subjects with a mean QTcF value >450 msec are not eligible to enter the Extension Phase.

6. Subjects with significant pathological findings on brain MRI including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary)
7. Subjects who have a "yes" answer to the Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation questions 4 or 5 at Visit 20 or Visit 21 or any suicidal behavior during the study prior to the start of the Extension Phase
8. Female subjects of childbearing potential who meet any of the follow criteria:
    a. Do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period and for 28 days after study drug discontinuation
    b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation
    c. Who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation
9. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Visit 20 or Visit 21
10. Subjects with medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
11. Any other clinically significant abnormal findings in vital signs, ECGs and laboratory tests that would, in the investigator's opinion, affect the subject's safety or interfere with study assessments during the Extension Phase

## STUDY DESIGN AND PLAN

The Extension Phase allows eligible subjects to receive elenbecestat 50 mg for up to 48 months (4 years).

Subjects who are enrolled in the Core Study will have the option to participate in the Extension Phase provided that they complete the Core Study (which includes 18 months of double-blind treatment and 12 weeks of Follow-up Period) and satisfy the entry criteria for the Extension Phase. Subjects who discontinue from study drug during the Core Study are not eligible to participate in the Extension Phase.

Eligible subjects who choose to participate in the Extension Phase may enter the Extension Phase immediately following the completion of Visit 20 (ie, Visit 21 procedures may be completed on the same day as Visit 20). Subjects who are eligible to participate in the Extension Phase but who do not transition to the Extension Phase on the day of Visit 20 may enter the Extension Phase any time within 4 weeks of Visit 20. The medical monitor must be contacted if Visit 21 is to occur more than 4 weeks after Visit 20. For all subjects, assessments performed at Visit 20 may serve as baseline values for the Extension Phase (ie, results of assessments conducted at Visit 21) with exceptions of laboratory assessments and vital signs, which must be repeated if Visit 21 occurs more than 10 days from Visit 20.

During the Extension Phase, subjects will receive open-label elenbecestat 50 mg per day for up to 48 months. Subjects with pending INR and serum pregnancy test results (females subjects of childbearing potential only) but who are otherwise qualified may begin Extension Phase dosing at Visit 21; however, these subjects must discontinue study drug treatment immediately if either test result meet the exclusion criteria.

Safety assessments will be performed as described in Table 14. Subjects may discontinue from study drug for any reason. Subjects who complete 48 months of the Extension Phase treatment or who discontinue the study drug must comply with the Early Discontinuation (ED) Visit (within 7 days after the last dose of study drug) and the Follow-up Visits (Weeks 4 and 12 after the last dose of study drug).

The study will end when the last visit for the last subject has completed the Extension Phase.

**Removal of Subjects from Therapy or Assessment**

The investigator may discontinue study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to stop study drug or withdraw from the study at any time for any reason. Subjects who discontinue study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. Subjects who discontinue from treatment during the Extension Phase will have 2 posttreatment Follow-up Visits at 4 and 12 weeks after the last dose of study drug.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug should be collected on the ED from study drug electronic case report form (eCRF) page (see Protocol Section 9.5.5). In addition, the date of last dose of study drug will be recorded on the Study Drug Dosing eCRF page.

Safety-related criteria for discontinuation of study drug include the following:

1. Absolute lymphocyte count will be monitored during the study. Should a subject develop lymphocytopenia (less than 800/mm$^3$ or LLN, whichever is higher), a confirmation test should occur as soon as possible but no later than within 5 days with a repeat test of absolute lymphocytes. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm$^3$) should be handled as above. If a 2nd occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm$^3$), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug.

2. A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), will be discontinued from study drug and a dermatologic consult will be requested regardless of whether the rash is considered drug-related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

3. Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

4. Pregnancy

5. A postdose ECG with a QTcF interval increase from baseline >60 msec and a QTcF interval >450 msec as demonstrated from triplicate ECGs

6. Subjects who develop of any of the following features on MRI should be discussed with the medical monitor: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. If discontinued from study drug, subjects will undergo an ED Visit within 7 days after discontinuation. They will also undertake an Unscheduled (UNS) Visit (with MRI) at approximately 4 weeks after the visit at

which such MRI features were first identified. Additional visits for safety may be arranged if clinically indicated in the opinion of the investigator, including after 12 weeks after the last dose of study drug. At any time during the Treatment Period, subjects who have asymptomatic, treatment-emergent microhemorrhages as detected by MRI, but none of the features which merit discontinuation of treatment (ie, vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic treatment-emergent microhemorrhage) may continue with treatment. These subjects will have safety assessments (including MRI) at approximately 4 weeks after the visit at which such MRI features were found. They will also continue with the scheduled MRI scans. Additional unscheduled MRI scans may be arranged on an individual subject basis in discussion with the study medical monitor.

7. Subjects who have postdose ECG with an average QTcF interval >500 msec from triplicate ECGs should be discussed with the medical monitor.

**Treatments**

During the Extension Phase, all subjects will receive open-label elenbecestat 50 mg once daily (QD). Each subject will take 1 tablet orally QD, with or without food. Please refer to Table 14 for specific information on drug administration on days when PD sampling is to be performed.

**EXTENSION PHASE ASSESSMENTS**

Safety assessments will continue to be monitored according to the Schedule of Assessments and all adverse events (AEs) and serious adverse events (SAEs) recorded. All safety assessments (eg, physical examinations, neurological examinations, vital signs, hematology, blood chemistry, serum and urine pregnancy test for females of childbearing potential, safety MRI and vMRI) will be performed as described in Table 14. The number of blood samples and the total volume of blood that will be collected throughout Extension Phase are summarized in Table 13.

There will be no centralized dermatological assessments in the Extension Phase; however, dermatological assessments will be performed by the investigator at every scheduled visit and as needed, at a UNS Visit. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregivers or informants will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly.

Full neurologic examinations will be performed at the start of the Extension Phase (Visit 20 or 21), and every 6 months during the first 24 months of the Extension Phase Treatment

Period and every 12 months thereafter. An additional neurologic examination will also be performed at the final Follow-up Visit. The neurologic examinations will include muscle strength testing and assessment of cranial nerves including olfaction, with the use of the Brief Smell Identification Test, as well as other parts of the central nervous system (CNS).

Complete blood counts and percentages will be measured (by a centralized laboratory) every scheduled visit. Additional blood sample will be collected and stored; these samples may be used for exploratory biomarker analyses or be analyzed in the event that the subject develops treatment-emergent adverse events (TEAEs) that warrant further investigation.

Peripheral blood mononuclear cells (PBMCs) will be collected at baseline (Visit 21), Month 6 (Visit 26), Month 12 (Visit 28), and Month 24 (Visit 32) only for exploratory immunomodulatory and immune-based analyses. These blood samples will be collected at the specified visits and stored in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

Safety brain MRI and vMRI assessments will be performed at Month 24 (Visit 32) and Month 48 (Visit 38) of the Extension Phase Treatment Period. Subjects who discontinue early from the Extension Phase will have safety brain MRI and vMRI assessments at the ED Visit if these assessments have not already been performed during the preceding 90 days. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Assessment of suicidal ideation and behavior using the C-SSRS will be performed at the start of the Extension Phase (Visit 21) and at Month 24 (Visit 32) and Month 48 (Visit 38) of the Extension Phase Treatment Period. Subjects who discontinue early from the Extension Phase will have assessments of suicidality using C-SSRS at the ED Visit. Clinical assessment of suicidality, collected from both the subject and the caregiver/informant, will be performed at every scheduled interim safety visit that do not include administration of the C-SSRS. At these visits, a positive suicidality assessment from the subjects or their caregiver/informant on the clinical assessment of suicidality (ie, “yes” response on the clinical assessment of suicidal thinking and behavior) will trigger the C-SSRS to be administered.

Blood sample for PD analyses will be collected at start of the Extension Phase (Visit 20 or 21), Month 12(Visit 28), Month 24 (Visit 32), Month 36 (Visit 35), and Month 48 (Visit 38 or ED Visit), and during the Follow-up Period (at 4 and 12 weeks after last dose of study drug in the Extension Phase). The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. The blood sample for PD analyses should be collected at fasting or at least 2 hours after the most recent meal.

Clinical assessments (MMSE and FAQ) will be administered every 3 months for the first 24 months and every 4 months thereafter, as described in Table 14.

The Follow-up Visit will take place at Weeks 4 and 12 after the last dose of study drug as described in Table 14. These assessments will also be performed if a subject prematurely discontinues from the Extension Phase.

**Table 13 Summary of Blood Sample Volumes for Extension Phase**

| Assessment | Total number of collection time points[a] | Number of time points x volume per collection (mL) | Total volume (mL) |
|---|---|---|---|
| | | Extension Phase Treatment and Follow-up Periods | |
| **Blood** | | | |
| Clinical Chemistry | 21 | 21 x 2 mL | 42 mL |
| Hematology | 21 | 21 x 5 mL | 105 mL |
| Lymphocyte subset analyses[b] | 8 | 8 x 4 mL | 32 mL |
| PBMC | 4 | 4 x 16 mL | 64 mL |
| PT, PTT for INR | 1 | 1 x 3 mL | 3 mL |
| Serum Pregnancy Test | 1 | 1 x 2 mL | 2 mL |
| Sample for immune status[c] | 10 | 10 x 4 mL | 40 mL |
| PD sample | 8 | 8 x 4 mL | 32 mL |
| Total volume whole blood collected | | | 320 mL |

PBMC = peripheral blood mononuclear cell, PT = prothrombin time, PTT = partial thromboplastin time, INR = International Normalized Ratio, PD = pharmacodynamics.

a: Total collection time points include a baseline sample at Visit 21 if not done at Visit 20; a baseline sample will be collected only if Visit 21 is conducted more than 10 days after Visit 20.

b: Blood samples for lymphocyte subset analyses will be collected and analyzed at every visit during the first 12 months only; reports of the analyses will be sent to the sponsor only.

c: Blood samples for immune status will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

## STUDY DRUG SUPPLIES

Elenbecestat (E2609) tablets of 50-mg dose strengths will be supplied. Each subject will take 1 tablet per day.

## SCHEDULE OF PROCEDURES/ASSESSMENTS

Table 14 presents the Schedule of Procedures/Assessments for the Extension Phase.

## Table 14 Schedule of Procedures/Assessments in Study 202: Extension Phase

| **Phase** | **Extension Phase** | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | | | | | | | **Follow-Up[d]** | | **UNS Visit[e]** |
| **Visit[a]** | **21[b]** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **30** | **31** | **32** | **33** | **34** | **35** | **36** | **37** | **38** | **ED[c]** | **Wk 4** | **Wk 12** | |
| **Ext Day** | **1** | **15** | **29** | **57** | **85** | **183** | **274** | **365** | **456** | **547** | **638** | **729** | **848** | **974** | **1093** | **1212** | **1338** | **1457** | | **1485** | **1541** | |
| **Ext Week** | **1** | **3** | **5** | **9** | **13** | **27** | **40** | **53** | **66** | **79** | **92** | **105** | **122** | **140** | **157** | **174** | **192** | **209** | | **213** | **221** | |
| **Weeks elapsed since 1st Ext dose** | **0** | **2** | **4** | **8** | **12** | **26** | **39** | **52** | **65** | **78** | **91** | **104** | **121** | **139** | **156** | **173** | **191** | **208** | | **212** | **220** | |
| **Nominal months elapsed since 1st Ext dose** | **0** | | **1** | **2** | **3** | **6** | **9** | **12** | **15** | **18** | **21** | **24** | **28** | **32** | **36** | **40** | **44** | **48** | | **49** | **51** | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | | | |
| Routine physical examination with dermatologic review | X[f,g] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[h] | X |
| Inclusion and Exclusion criteria | X | | | | | | | | | | | | | | | | | | | | | |
| Vital signs, including respiratory rate[i] | X[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[h] | X |
| Weight | X[f] | | | | | | | X | | | | X | | | X | | | X | X | | | X |
| Neurological examination[k] | X[f] | | | | | X | | X | | X | | X | | | X | | | X | X | | X | X |
| Concomitant medications[l] | X[m] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG[n] | X[f] | | | | X | X | | X | | X | | X | | | X | | | X | X | X | X[h] | X |
| Clinical biochemistry and urinalysis | X[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete blood | X[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| **Phase** | **Extension Phase** | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | | | | | | | **Follow-Up[d]** | | **UNS Visit[e]** |
| **Visit[a]** | **21[b]** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **30** | **31** | **32** | **33** | **34** | **35** | **36** | **37** | **38** | **ED[c]** | **Wk 4** | **Wk 12** | |
| **Ext Day** | **1** | **15** | **29** | **57** | **85** | **183** | **274** | **365** | **456** | **547** | **638** | **729** | **848** | **974** | **1093** | **1212** | **1338** | **1457** | | **1485** | **1541** | |
| **Ext Week** | **1** | **3** | **5** | **9** | **13** | **27** | **40** | **53** | **66** | **79** | **92** | **105** | **122** | **140** | **157** | **174** | **192** | **209** | | **213** | **221** | |
| **Weeks elapsed since 1st Ext dose** | **0** | **2** | **4** | **8** | **12** | **26** | **39** | **52** | **65** | **78** | **91** | **104** | **121** | **139** | **156** | **173** | **191** | **208** | | **212** | **220** | |
| **Nominal months elapsed since 1st Ext dose** | **0** | | **1** | **2** | **3** | **6** | **9** | **12** | **15** | **18** | **21** | **24** | **28** | **32** | **36** | **40** | **44** | **48** | | **49** | **51** | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | | | |
| count | | | | | | | | | | | | | | | | | | | | | | |
| Blood sample for PT and PTT for INR | X | | | | | | | | | | | | | | | | | | | | | |
| Blood samples for lymphocyte subset analysis[o] | X[j] | X | X | X | X | X | X | X | | | | | | | | | | | | | | |
| Blood samples for PD and exploratory biomarkers[p] | X[f] | | | | | | | X | | | | X | | | X | | | X | X | X | X | X |
| Blood samples (isolation of PBMCs) | X[f] | | | | | X | | X | | | | X | | | | | | | | | | |
| Urine pregnancy test (females of CBP only)[q] | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Serum pregnancy test (females of childbearing potential only) | X | | | | | | | | | | | | | | | | | | | | | X |
| Blood sample (storage for | X[f] | | X | | X | X | | X | | | | X | | | | | | X | X | X | X | X |

| Phase | Extension Phase | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | | | | | | | **Follow-Up[d]** | | **UNS Visit[e]** |
| **Visit[a]** | **21[b]** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **30** | **31** | **32** | **33** | **34** | **35** | **36** | **37** | **38** | **ED[c]** | **Wk 4** | **Wk 12** | |
| **Ext Day** | **1** | **15** | **29** | **57** | **85** | **183** | **274** | **365** | **456** | **547** | **638** | **729** | **848** | **974** | **1093** | **1212** | **1338** | **1457** | | **1485** | **1541** | |
| **Ext Week** | **1** | **3** | **5** | **9** | **13** | **27** | **40** | **53** | **66** | **79** | **92** | **105** | **122** | **140** | **157** | **174** | **192** | **209** | | **213** | **221** | |
| **Weeks elapsed since 1st Ext dose** | **0** | **2** | **4** | **8** | **12** | **26** | **39** | **52** | **65** | **78** | **91** | **104** | **121** | **139** | **156** | **173** | **191** | **208** | | **212** | **220** | |
| **Nominal months elapsed since 1st Ext dose** | **0** | | **1** | **2** | **3** | **6** | **9** | **12** | **15** | **18** | **21** | **24** | **28** | **32** | **36** | **40** | **44** | **48** | | **49** | **51** | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | | | |
| immune status)[r] | | | | | | | | | | | | | | | | | | | | | | |
| MMSE[s] | X[f] | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| FAQ[s] | X[f] | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| C-SSRS | X[f] | | | | | | | | | | | X | | | | | | X | X | | | X |
| Clinical assessment of suicidal thinking and behavior[t] | | X | X | X | X | X | X | X | X | X | X | | X | X | X | X | X | | | X | X | X |
| Safety MRI and vMRI[u] | X[f] | | | | | | | | | | | X | | | | | | X | X | | | X |
| Adverse events | X[m] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dispense study drug | X[v] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |

**Notes for Table 14**

C-SSRS = Columbia Suicide Severity Rating Scale, ED = Early Discontinuation, Ext = Extension Phase, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), INR = International Normalized Ratio; MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, QTcF = QTc with Fridericia correction; UNS = unscheduled, vMRI = volumetric magnetic resonance imaging, Wk = week.

a: A window of ±3 days will be permitted for Visits 22 and 23. A window of ±7 days will be permitted for Visits 24 and 25. A window of ±10 days will be permitted for Visit 26 to 38 inclusive. A window of ±3 days will be permitted for the Follow-up Visits. If a permitted visit window is used, every effort should be made to bring the

subject back in line with the "weeks elapsed since 1st dose in Extension Phase" at subsequent visits.

b: Visit 21 may occur on the same day or within 4 weeks of Visit 20 date. The Medical Monitor must be contacted if Visit 21 is to occur more than 4 weeks after Visit 20. Informed consent must be obtained before performing Visit 21 assessments.

c: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-up Visits will be scheduled 4 and 12 weeks after the last dose of study drug.

d: All subjects, regardless of whether they complete all 48 months of treatment or discontinue study drug prematurely, will complete the 2 posttreatment Follow-up Visits; (ie, 4 and 12 weeks after the last dose of study drug). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-up Period.

e: Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

f: Result from Visit 20 will also serve as Visit 21 result. If the specified assessment was not performed at Visit 20, it must be performed at Visit 21.

g: Dermatologic assessment by the investigator must be performed at Visit 21 in addition to the centralized skin assessment (using standardized photography) performed at Visit 20.

h: Only if clinically significant abnormalities are found at the Follow-up Week 4 Visit and the investigator considers it necessary to repeat at the Follow-up Week 12 Visit.

i: Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

j: Result from Visit 20 will also serve as Visit 21 result if Visit 21 occurs within 10 days from Visit 20. If Visit 21 occurs more than 10 days after Visit 20, the assessment must be repeated at Visit 21.

k: Examples of neurological signs that may indicate new central nervous system pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. The Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits and serves as part of the neurologic examination.

l: Please refer to Section 9.4.7, which describes prohibited and permitted medications in the study.

m: Result from Visit 20 will also serve as Visit 21 result if Visit 21 occurs on the same day as Visit 20. If Visit 21 occurs more than 1 day after Visit 20, the assessment must be repeated at Visit 21.

n: Single 12-lead standard ECGs will be recorded. If the QTcF is greater than 450 msec, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

o: Reports of the lymphocyte subset analyses will be sent to the sponsor only. Lymphocyte subsets will include but are not limited to the following cell surface marker assessments: CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [NK cells] and CD14 [macrophages]) and absolute lymphocytes. Regulatory T cells will also be measured. Viability staining may also be employed.

p: PD blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day. All PD blood samples should be collected predose.

q: If dipstick urinalysis performed at site is abnormal,a serum pregnancy test should be performed.

r: Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior

exposure to any suspected infective agents.

s: The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws).

t: The clinical assessment of suicidality will require input from both the subject and the caregiver/informant. A positive suicidality assessment from the subject or their caregiver/informant on the clinical assessment of suicidality (ie, a "yes" response on the clinical assessment of suicidal thinking and behavior) will trigger the C-SSRS to be administered.

u: MRI imaging will be conducted on separate days from the scheduled visits. Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images in MRI will be read by an approved central reader. MRI imaging should be conducted within 7 days before Visits 21 (where applicable), 32, and 38. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

v: The subject will take the first dose of study drug at the study site and the subject will be encouraged to stay at the site for an appropriate period of time as determined by the investigator or Safety Physician for postdose medical observation. Subjects with pending INR and serum pregnancy results may begin dosing at Visit 21 if they satisfy all other Extension Phase entry criteria.

## EXTENSION PHASE STATISTICAL METHODS

### Primary Endpoint

- Safety endpoints: AE, vital sign, ECG, physical examination, clinical laboratory test, any relevant test of cognitive function to evaluate decline, and MRI parameter (microhemorrhage, vasogenic edema, and other clinically significant abnormalities).

### Secondary Endpoint

Changes from Core Study and Extension Phase baselines in

- MMSE and FAQ at each visit assessed in the Extension Phase
- Plasma amyloid measurements at 12,24, 36, and 48 months of Extension Phase treatment
- vMRI parameters including, but not limited to, total hippocampal volume, left and right hippocampal volume, whole brain volume, and total ventricular volume with up to 24 and 48 months of Extension Phase treatment

## EXTENSION PHASE ANALYSIS SETS

- The **Extension Phase Safety Analysis Set (OLE-SAS)** is the group of subjects who receive at least 1 dose of study drug during the Extension Phase and who had any on therapy safety data during Extension Phase.
- The **Extension Phase Full Analysis Set (OLE-FAS)** is the group of subjects who receive at least 1 dose of study drug during the Extension Phase and have at least 1 postdose efficacy assessment during the Extension Phase.
- The **Extension Phase PD Analysis Set** is the group of subjects who have at least 1 posttreatment PD measurement in the Extension Phase.

### Safety Analyses

Safety analysis will be performed similarly to the Core Study. All safety analyses will be based on OLE-SAS. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS and clinical assessment of suicidality), and changes from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements, and cognitive decline assessment such as MMSE will be summarized by using descriptive statistics.

**Efficacy Analyses**

The following secondary efficacy endpoints will be summarized by descriptive statistics and/or graphs, using OLE-FAS:

- Changes from Core Study and Extension Phase baselines in MMSE and FAQ scores
- Changes from Core Study and Extension Phase baselines in vMRI parameters including, but not limited to, total hippocampal volume, left and right hippocampal volume, whole brain volume, and total ventricular volume at 24 and 48 months

The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

**Pharmacodynamic Analyses**

The OLE PD Analysis Set will be used for the summaries and analyses of PD biomarkers. The percentage change in plasma amyloid measurements from Core Study and Extension Phase baselines to 12, 24, 36, and 48 months of Extension Phase treatment will be analyzed and presented graphically.

**SAMPLE SIZE RATIONALE**

Subjects who complete the Core Study will have the option to participate in the Extension Phase. There is no sample size calculation for the Extension Phase.

# PROTOCOL SIGNATURE PAGE

(revised per Amendment08)

**Study Protocol Number:** E2609-G000-202
**Study Protocol Title:** A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of Elenbecestat (E2609) in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01 and 05)
**Investigational Product Name:** Elenbecestat (E2609)
**IND Number:** 109308
**EudraCT Number:** 2014-002723-94

**SIGNATURES**
Authors:

PPD
PPD Neurology Business Group, Eisai Ltd — Date

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PPD Neurology Business Group, Eisai Inc. — Date

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PPD Neurology Business Group, Eisai Inc. — Date

PPD
PPD Neurology Business Group, Eisai Inc. — Date

# INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of Elenbecestat (E2609) in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01 and 05) |
| **Investigational Product Name:** | Elenbecestat (E2609) |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

| Investigator | Signature | Date |
|---|---|---|

# REVISION HISTORY

**Revisions to Version 8.0**

**New version/date: Version 9.0/01 Feb 2017 (per Amendment 07)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| An editorial revision was made to add "elenbecestat", the proposed International Nonproprietary Name (pINN) for "E2609"; grammatical, typographical, and formatting changes were also made. | The revision was made to provide consistency for current and future elenbecestat (E2609) clinical development documents. | All sections of the protocol that previously included "E2609" or required editorial revision |
| A Open-label Extension (OLE) Phase of up to 24 months was added to the protocol specifying that eligible subjects who elect to continue open-label treatment after completing Visit 20 will receive elenbecestat (E2609) 50 mg per day. A detailed description of the OLE Phase was added in Appendix 6.<br><br>An editorial revision was made referring to the original "study" (Prerandomization amd Randomization Phases) as the "Core Study". | The OLE was added to assess long-term safety and tolerability of elenbecestat (E2609) 50 mg per day in subjects who elect to continue open-label treatment after Visit 20.<br>The editorial revision was made for clarity of presentation where description of the OLE procedures have been added. | Synopsis<br>• Study Period and Phase of Development<br>• Objectives<br>• Study Design<br>• Inclusion Criteria<br>• Exclusion Criteria<br>• Study Treatment<br>• Duration of Treatment<br>• Concomitant Drug/Therapy<br>• Assessments<br>• Endpoints<br>• Analysis Sets<br>• Analyses<br>Section 7<br>Section 8<br>Section 9.1<br>Section 9.2.4.3<br>Section 9.2.4.4<br>Section 9.2.5<br>Section 9.3<br>Section 9.3.3<br>Section 9.4.1<br>Section 9.4.7<br>Section 9.5.1.2.1<br>Section 9.5.1.3.1<br>Section 9.5.1.3.2<br>Section 9.5.1.4.2 |

**Revisions to Version 8.0**

**New version/date: Version 9.0/01 Feb 2017 (per Amendment 07)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | | Section 9.5.1.5<br>Section 9.5.2<br>Section 9.5.4.1<br>Section 9.5.5<br>Section 9.7.1<br>Appendix 6 |
| Addition of the OLE Phase to evaluate the long-term safety and tolerability of elenbecestat (E2609) and cross reference to the detailed OLE Phase protocol in Appendix 6. | To add the OLE Phase in the context of the elenbecestat (E2609) clinical development program and study design to provide investigators with the location of the complete detailed OLE Phase protocol. | Section 7<br>Section 9.1<br>Section 9.1.3 |
| Addition of cross reference to objectives for OLE Phase protocol in Appendix 6. | To provide investigators with the location of the OLE Phase objectives. | Section 8 |
| Safety aspects have been built into the study design in light of the preclinical and clinical safety data with elenbecestat (E2609) to mitigate clinical risk are extended to the OLE Phase and 2 off-treatment Follow-Up Visits at 4 and 12 weeks after the last dose of study drug during the OLE Phase are added. | To provide instruction to investigators for continued monitoring procedures for mitigation of potential clinical risk associated with elenbecestat (E2609). | Section 9.2.5<br>Section 9.3.3<br>Section 9.5.1.5.7<br>Section 9.5.5 |
| Addition of requirement that subjects meet all inclusion criteria and not meet any of the exclusion criteria for the OLE Phase, with cross reference to the criteria for the OLE Phase in Appendix 6. | To provide investigators with the requirements for subject elegibility and the location of the OLE Phase inclusion and exclusion criteria. | Section 9.3 |
| Addition of cross reference to criteria for discontinuation of study drug during the OLE Phase in Appendix 6. | To provide investigators with the location of the criteria for discontinuation of study drug during the OLE Phase. | Section 9.3.3 |
| Prior and concomitant therapy restrictions are extended to the OLE Phase. | To provide instruction to investigators for prior and concomitant therapy during the OLE Phase. | Section 9.4.7 |

**Revisions to Version 8.0**

**New version/date: Version 9.0/01 Feb 2017 (per Amendment 07)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Addition of cross reference to Table 14. | To direct the investigators to the detailed OLE Phase Schedule of Procedures/Assessments in Study 202: Open-label Extension Phase (Visit 21 through Visit 32). | Section 9.5.1.2.1<br>Section 9.5.1.3.1<br>Section 9.5.1.3.2<br>Section 9.5.1.4.2<br>Section 9.5.1.5<br>Section 9.5.1.5.1<br>Sections 9.5.1.5.3 to 9.5.1.5.11<br>Section 9.5.2<br>Section 9.5.5 |
| Addition of requirement to report all adverse events (AEs) observed during the OLE Phase; clarification that Visit 20 is the last visit for subjects who do not enter the OLE Phase and that Visit 34 is the last study visit for subjects who enter the OLE Phase. | Added for clarification. | Section 9.5.1.5.1 |
| Removed instructions for SAE reporting outside of the reporting period. | To match the standard template for SAE reporting. | Section 9.5.1.5.1 |
| Addition of ECG Assessments during the OLE Phase. | To specify that a single 12-lead ECG will be performed during the OLE Phase. | Section 9.5.1.5.6 |
| Addition of Dermatologic Assessments during the OLE Phase. | To stipulate that evaluation of skin assessments will be performed by the investigator during the OLE Phase. | Section 9.5.1.5.8 |

**Revisions to Version 8.0**

**New version/date: Version 9.0/01 Feb 2017 (per Amendment 07)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Addition of requirement to report all serious adverse events (SAEs) observed during the OLE Phase; clarification that Visit 20 is the last visit for subjects who do not enter the OLE Phase and that Visit 34 is the last study visit for subjects who enter the OLE Phase. | Added for clarification. | Section 9.5.4.1 |
| Addition of cross reference to Appendix 6 for discussion of OLE Phase statistical analyses. | To provide investigators the location of the OLE Phase statistical analyses discussion. | Section 9.7.1 |
| The term "total lymphocyte count" was changed to "absolute lymphocyte count". | To ensure consistency throughout the protocol and consistency with reports generated by the central laboratory. | Synopsis<br>• Concomitant Drug/Therapy<br>Section 9.2.5<br>Section 9.4.7<br>Section 9.5.1.5.3<br>Table 7<br>Appendix 2 |

**Revisions to Version 7.0**

**New version/date: Version 8.0/02 Nov 2016 (per Amendment 06)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Subjects currently receiving 5 or 15 mg elenbecestat (E2609) will be re-assigned to 50 mg elenbecestat (E2609) for the remainder of the double-blind treatment period provided they will receive at least 12 weeks of double-blind treatment after the re-assignment, (ie, no dose reassignments past Visit 17). | As elenbecestat (E2609) 50 mg has been selected as the appropriate dose for Phase 3 development, subjects should not continue with doses that are not being advanced clinically. Additionally, the re-assignment of subjects in elenbecestat (E2609) 5 and 15 mg to elenbecestat (E2609) 50 mg will further the safety and tolerability data in subjects exposed to elenbecestat (E2609) 50 mg. | Synopsis<br>• Study Design<br>• Number of Subjects<br>• Sample Size Rationale<br>Section 7.1<br>Section 9.1<br>Section 9.1.2.1<br>Section 9.4.1<br>Section 9.4.4<br>Section 9.5.2 |
| Clarified that one of the exploratory endpoints will analyze change from baseline in CSF amyloid and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment only. There will no analysis for treatment follow-up. | Correction | Synopsis<br>• Analysis for Exploratory Endpoints<br>• Exploratory Objective<br>Section 8.3<br>Section 9.7.1.1.3<br>Section 9.7.1.6.3 |
| The frequency of DSMB safety reviews after the 12 week interim safety analysis will be reassessed and details will provided in the DSMB charter. | The DSMB charter will provide full details of interim safety reviews. | Synopsis<br>• Study Design<br>Section 9.1 |
| Removed the statement that subjects must be stable on acetylcholinesterase inhibitor (AChEI) or mementine to be included in the primary analyses. | This statement is no longer relevant as of Amendment 05. | Synopsis<br>• Concomitant Drug/Therapy<br>Section 9.4.7 |
| Added a statement to specify that additional analyses will be performed for subjects with dose re-assignment and details of these analyses and treatment group definitions will be provided in the statistical analysis plan (SAP); clarified that the SAP will be finalized before database lock. | To clarify that the SAP will be finalized prior to database lock and it will provide full details of the analyses to be performed for this study. | Section 9.7.1 |

**Revisions to Version 6.0**

**New version/date: Version 7.0/26 Sep 2016 (per Amendment 05)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Grammatical, typographical, and formatting changes | | Throughout |
| Removed Stage B from protocol. In line with this decision, the study objectives and endpoints have been modified and subjects who discontinue study drug early for any reason will no longer be required to complete efficacy visits after last dose of study drug. | This study will no longer be a Proof-of-Concept study. | Synopsis<br>• Study Protocol Title<br>• Investigators<br>• Sites<br>• Study Period and Phase of Development<br>• Objectives<br>• Study Design<br>• Early Discontinuation<br>• Number of Subjects<br>• Study Treatments<br>• Efficacy Assessments<br>• Safety Assessments<br>• Statistical Methods<br>• Study Endpoints<br>• Analysis Sets<br>• Efficacy and Biomarker Analyses<br>• Analysis for the Primary/Secondary/Exploratory Endpoints<br>• Pharmacokinetic Analyses<br>• Pharmacokinetic /Pharmacodynamic Analyses<br>• Interim Analyses<br>• Sample Size Rationale<br>Section 6<br>Section 7<br>Section 8<br>Section 8.3<br>Section 9.1<br>Section 9.2.1<br>Section 9.2.3<br>Section 9.2.4.4<br>Section 9.2.5<br>Section 9.3 |

**Revisions to Version 6.0**

**New version/date: Version 7.0/26 Sep 2016 (per Amendment 05)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | | Section 9.4.3<br>Section 9.4.4<br>Section 9.4.7<br>Section 9.2.5<br>Section 9.5.1.3.1<br>Section 9.5.1.4.2<br>Section 9.5.1.5.1<br>Section 9.5.2<br>Section 9.5.4.1<br>Section 9.5.5<br>Section 9.7<br>Section 10 |
| Updated Eisai contact information | Change in personnel and move to Building 100 | • Title Page<br>• Protocol Signature Page |

**Revisions to Version 5.0**

**New version/date: Version 6.0/29 Jun 2016 (per Amendment 04)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised number of investigational sites (from 40 to 35) | Feasibility | • Synopsis -<br>o Study Design<br>o Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Removed Exclusion Criterion No. 44 for male subjects regarding restrictions on child bearing | No longer a safety concern; E2609 has not shown a deleterious effect on sperm in preclinical reproductive toxicity studies. | • Synopsis:<br>o Exclusion Criteria<br>• Section 9.3.2 |
| Added option for subjects who provided a CSF sample prior to randomization but who declined the CSF sample collection after 4 weeks of dosing to provide a postdose CSF sample at any point in the study (ie, even after 4 weeks of dosing). | Reflects the added value of CSF data for the PK/PD secondary objective of this study. In addition, given that PK steady state is achieved within the 1st 2 weeks of initiation of dosing, data collected post Week 4 visit is still considered to be applicable in assessment of the steady state effect. | • Synopsis -<br>o Pharmacodynamic Assessments<br>• Section 5.3<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.5.1.3.3<br>• Section 9.5.1.4<br>• Table 6<br>• Table 7<br>• Table 8 |
| Revised details of restrictions to anticoagulant therapy and short-term steroid use revised/moved details regarding antiplatelet drugs to the main body of the protocol | To assist in subject recruitment and retention and considering that the strict restrictions were not necessary for subject safety | • Synopsis -<br>o Concomitant Drug/Therapy<br>• Section 9.4.7<br>• Appendix 2 |
| Removed the >33% decrease from baseline for CD4, CD8, and CD19 as a trigger for more frequent testing of flow cytometry and CBCs. Additional safety monitoring for CD4, CD8, CD19, and CBCs will only be based on the population adjusted LLNs for clinically asymptomatic subjects. | Experience to date has indicated significant variability within the normal range, both for increases and decreases. Absolute counts of lymphocyte subsets are more meaningful than percentage decreases for triggering more frequent monitoring. | • Section 9.3.3<br>• Table 1<br>• Table 2 |

**Revisions to Version 5.0**

**New version/date: Version 6.0/29 Jun 2016 (per Amendment 04)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Added option to temporarily suspend study drug for subjects who are clinically asymptomatic but who meet CD4, CD8, or CD19 discontinuation thresholds on 2 consecutive tests. Introduce rules for ability to re-start study drug (ie, rechallenge) in these subjects. Only 1 cycle of temporary suspension and rechallenge with study drug permitted for any individual subject. | To assist in subject retention and to gain knowledge on the behavior of lymphocyte subsets on rechallenge. | • Section 9.3.3<br>• Table 1<br>• Table 2 |
| Added extra blood draw times with focus on lymphocyte subsets, CBCs, and immunoglobulins during the 12-week safety follow-up for all subjects. | To increase frequency of key safety monitoring parameters in post-treatment follow-up period so as to assess immunological changes after completion of study drug | • Synopsis<br>o Study Design<br>o Safety Assessments<br>• Section 9.1.2.2<br>• Section 9.1.2.3<br>• Section 9.2.5<br>• Section 9.3.3<br>• Table 7<br>• Table 8<br>• Section 9.5.1.5.7<br>• Section 9.5.5 |
| Clarified that the Functional Assessment Questionnaire is to be administered to the informant/caregiver, and not the subject. | Clarification | • Synopsis<br>o Efficacy Assessments<br>• Section 9.5.1.3.1 |
| Added clarification that the Brief Smell Identification Test will be administered as part of the neurological examination | Clarification | • Synopsis<br>o Safety Assessments<br>o Interim Analyses<br>• Section 9.1.1.2<br>• Section 9.5.1.2.1<br>• Section 9.5.1.5.9<br>• Table 6<br>• Table 7 |

**Revisions to Version 5.0**

**New version/date: Version 6.0/29 Jun 2016 (per Amendment 04)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised number of randomized subjects in Stage A to n=60±20% | To allow for additional randomization based upon current number of subjects in screening at the time of amendment implementation | • Synopsis<br>  ○ Study Design<br>  ○ No. of Subjects<br>• Section 7<br>• Section 9.1<br>• Section 9.2.1<br>• Section 9.2.5<br>• Section 9.3<br>• Section 9.7.3 |
| Grammatical, typographical, and formatting corrections | Consistency | various |

**Revisions to Version 4.0**

**New version/date: Version 5.0, 06 Feb 2016 (per Amendment 03)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Add interim analyses of safety, and PK/PD data throughout Stage A | Decision making regarding the remainder of the study and the full elenbecestat (E2609) clinical development program | • Synopsis –<br>o Exploratory Endpoint Analysis<br>o Interim Analysis<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.4.6<br>• Section 9.7.1.7.1 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Grammatical, typographical, and formatting changes | | Throughout |
| Mandatory nature of CSF collection in study changed to voluntary. This change impacts the timing and details of the PK/PD interim analyses. It also impacts the nature of the CSF-related objectives, which will now be identified as exploratory. | To increase rate of subject consent into the study | • Synopsis –<br>o Secondary Objectives<br>o Exploratory Objectives<br>o Study Design<br>o Exclusion Criterion No. 12<br>o Pharmacokinetic Assessments<br>o Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments<br>o Safety Assessments<br>o Secondary Endpoints<br>o Exploratory Endpoints<br>o Analysis for the Secondary Endpoints<br>o Analysis for the Exploratory Endpoints<br>• Section 5.3<br>• Section 8.2<br>• Section 8.3<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.2.5<br>• Section 9.3.2<br>• Section 9.4.6<br>• Section 9.5.1.3.3<br>• Section 9.5.1.4<br>• Section 9.5.1.5.12<br>• Section 9.7.1.1.2<br>• Section 9.7.1.1.3<br>• Section 9.7.1.6.2<br>• Section 9.7.1.6.3<br>• Appendix 2, Listing 2 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Extended the range of cognitive impairment in delayed recall that would be considered inclusionary for the study and removed the eligibility nature of the cognitive tests repeated at the Baseline Visit. | Original delayed recall aspect of inclusion criterion #1 was considered to be too restrictive and was unnecessarily screening out subjects with MCI/prodromal AD. The eligibility nature of the cognitive tests repeated at the Baseline Visit has been removed in order to simplify the requirements of the pretreatment period for the study. | • Synopsis –<br>  ○ Inclusion/ Exclusion Criteria<br>• Section 9.3.1<br>• Section 9.3.2 |
| Addition of historical amyloid PET scans for determination of eligibility for the study. Subjects with historical PET scans will not be part of the longitudinal PET analyses and therefore will not require a second PET scan at either Visit 18 or ED. | To provide the sites with greater operational flexibility and reduce subject burden. | • Synopsis –<br>  ○ Inclusion/Exclusion<br>  ○ Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments<br>• Section 9.1.1<br>• Section 9.2.4.3<br>• Section 9.3.1<br>• Section 9.5.2<br>• Table 6<br>• Table 7 |
| Added the need for safety laboratory tests to be repeated for subjects whose pre-treatment period is extended due to active infection. | To ensure that all baseline safety laboratory tests are repeated for subjects whose pretreatment period is extended. | • Synopsis –<br>  ○ Inclusion/Exclusion<br>• Section 9.3.2<br>• Section 9.5.2<br>• Table 6 |
| Clarified that exclusion criterion No. 22 (exclusion of subjects with CD4, CD8, or CD19 absolute counts below the LLN) applies to flow cytometry tests conducted at both the Screening and the Baseline Visits. Furthermore, LLNs that are adjusted for the subject population under study will be used. | It was not clear that Exclusion Criterion No. 22 applied to both the Screening and the Baseline Visits. The LLNs for CD4, CD8 and CD19 absolute counts require adjustment for the age of the patient population in this study. | • Synopsis –<br>  ○ Inclusion/ Exclusion Criteria<br>• Section 9.3.2 |
| Provided additional detail | Added to provide clarity | • Synopsis – |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| regarding scope of Exclusion Criterion No. 34 which excludes subjects with hypopigmentation conditions. | for the sites. | ○ Exclusion Criteria<br>• Section 9.3.2 |
| Revised number of clinical sites from 30 to 40 | For feasibility purposes | • Synopsis –<br>○ Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Relaxed the requirement for the cognitive assessments at Screening Visit 1 to be conducted in a certain order and revised the recommended order in which the assessments could be conducted. | To provide the sites with greater operational flexibility. | • Section 9.1.1<br>• Figure 2<br>• Section 9.5.1.3.1<br>• Section 9.5.2<br>• Table 6 |
| Clarify the duration for which the Safety magnetic resonance imaging (MRI) scan, the amyloid PET scan and the lumbar puncture (LP) collected CSF conducted at Screening are considered valid. | To provide sites with greater operational flexibility, particularly for re-screening of screen fail subjects. | • Section 9.1.1 |
| Clarify that for subjects meeting criteria for weekly monitoring of lymphocyte subsets, these can be accommodated within the scheduled clinic visits during the early stages of the treatment period of the study. | To provide operational clarity to the sites. | • Synopsis –<br>○ Exclusion Criteria<br>• Section 9.3.2<br>• Section 9.3.3<br>• Section 9.5.1.5.3 |
| Added the requirement for complete blood counts (CBC) with differentials to be performed whenever repeat or unscheduled flow cytometry tests are performed. | Such that CBC data are available at all times when flow cytometry data is available. | • Section 9.3.3<br>• Table 1<br>• Section 9.5.2<br>• Table 6<br>• Table 7 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Added 30 day window to the duration of the pre-treatment period if required for medical or operational reasons. | To provide the sites with greater operational flexibility. | • Synopsis –<br>  ○ Study Design<br>  ○ Duration of Treatment<br>• Section 9.1<br>• Figure 1<br>• Section 9.1.1<br>• Section 9.1.1.2<br>• Section 9.5.2<br>• Table 6 |
| Clarified the timing of the start of the Randomization Phase | Clarification | • Section 9.1.1<br>• Section 9.1.2<br>• Section 9.5.2<br>• Table 6<br>• Table 7 |
| Increased number of MCI/Prodromal or mild to moderate AD subjects screened for entry into the study | To reflect the higher screen failure rate than originally anticipated | • Synopsis –<br>  ○ Number of Subjects |
| Removal of CD127 cell surface markers | FoxP3 is the most accepted marker to measure T regulatory cells and additional assessment of CD127 is not required. | • Section 9.5.1.5.3<br>• Table 4<br>• Section 9.5.2.1 |
| Made the clinical biochemistry, urinalysis, CBC, lymphocyte subsets, and immunoglobulin tests mandatory at Visit 20, regardless of clinical significance at Visit 19. | For more comprehensive safety data at the second follow-up visit. | • Section 9.5.2<br>• Table 7 |
| Corrected reference to Exclusion Criterion No. 20 (and not to Exclusion #19) in footnote to Table 6 and Table 7 regarding timing of Visit 3 in relation to Visit 2. | Correction | • Section 9.5.2<br>• Table 6<br>• Table 7 |
| Revised details regarding prohibited antiplatelet drugs | To distinguish between those subjects who consent to CSF sample collection and those who do not | • Appendix 2, Listing 2 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015 (per Amendment 01)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised inclusion to allow for enrollment of mild to moderate AD subjects in Stage A and expand the Stage B mild AD cohort to also include moderate AD subjects | To collect safety data in a wider range of AD patients. | • Title Page<br>• Synopsis –<br>  o Objectives<br>  o Study Design<br>  o Number of Subjects<br>  o Inclusion/Exclusion Criteria<br>  o Study Treatments<br>  o Efficacy Assessments<br>  o Study Endpoints<br>  o Efficacy Analyses<br>  o Interim Analyses<br>  o Adaptive Randomization<br>  o Sample Size<br>• Section 5.3<br>• Section 7<br>• Section 8 (and all subsections)<br>• Section 9.1<br>• Section 9.1.1<br>• Figure 1<br>• Section 9.2.1<br>• Section 9.2.2<br>• Section 9.2.3<br>• Section 9.2.4.3<br>• Section 9.2.4.4<br>• Section 9.3<br>• Section 9.3.1<br>• Section 9.3.2<br>• Section 9.4.1<br>• Section 9.4.3<br>• Section 9.4.4<br>• Section 9.5.1.3.1<br>• Section 9.7.1.1.2<br>• Section 9.7.1.1.3<br>• Section 9.7.1.4<br>• Section 9.7.1.6<br>• Section 9.7.1.6.2<br>• Section 9.7.1.6.3<br>• Section 9.7.1.8.2<br>• Section 9.7.3<br>• Section 9.7.4 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015 (per Amendment 01)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised inclusion criteria for MMSE to ≥16 from ≥20 | The MMSE score is used as a cut-off for the most impaired subject that would be eligible for the study. Lowering the MMSE inclusion from ≥20 to ≥16 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD cohort. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.1 |
| Revised inclusion criteria for FAQ to ≤24 from ≤20 | As for the MMSE, the FAQ score is used as a cut-off for the most impaired subject that would be eligible for the study. Revising the FAQ inclusion from ≤20 to ≤24 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD cohort, and is consistent with an MMSE inclusion of ≥16. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.1 |
| Revised exclusion criteria such that small arachnoid cysts are not necessarily exclusionary | Arachnoid cysts are a common finding in otherwise healthy subjects. Small lesions (<1 cm in diameter) are generally not considered clinically significant and if discovered incidentally no long term follow up is routinely required. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised exclusion criteria for Ig (IgG, IgA, or IgM) to specify that levels below the LLN at Screening or Baseline need not be exclusionary | For subjects with a Screening or Baseline IG level <LLN to be considered for continuation in the study, assessment of clinical significance of the finding will be required. A finding of "not clinically significant" must be agreed between the Investigator and Medical Monitor in order for the subject to continue in the study. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised text to provide instructions for subject assent and associated consent by a legal representative for subjects who the Investigator considers not to have the capacity to consent themselves | With the expansion of the patient population to include moderately demented subjects it was necessary to provide directions regarding the consenting process for subjects considered to be lacking the | • Section 5.3 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015 (per Amendment 01)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | capacity to consent themselves. | |
| Revised number of clinical sites to 30 from 25 | For feasibility purposes. | • Synopsis –<br>  ○ Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Added allowance for Tier 1 and Tier 2 screening assessments to be performed on the same day | Added to provide operational clarity for the sites. | • Section 9.1.1.1<br>• Table 6 |
| Removed requirements for MRIs to include sequences for resting state functional MRI | This was an error and should not have been included in the original protocol. | • Table 6<br>• Table 7 |
| Revised text to clarify that on visits where CSF collection takes place, the CSF collection need not take place on the same day as the cognitive testing for that visit | Added to provide operational clarity for the sites. | • Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised text to clarify that the most important efficacy assessment to keep blinded from safety data is the CDR. | Added to provide operational clarity for the sites. | • Synopsis –<br>  ○ Safety Assessments<br>• Section 9.4.6<br>• Section 9.5.1.5 |
| Revised text to allow PK blood sample and PD blood samples to be taken either shortly before or shortly after the LP on CSF days | Added to provide operational flexibility for the sites. | • Section 9.5.1.4.1<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised Sponsors Grading for Laboratory Values for the following analytes: lymphocytes, neutrophils, albumin, creatinine, phosphate, and potassium serum-high (hyperkalemia) | Corrections made to align with the values for grading used by the central clinical laboratory for this study. | • Appendix 1 |
| Revised details regarding prohibited antiplatelet drugs | Previous version incorrectly referenced a biomarker subgroup. All subjects in this study will need to provide CSF samples. | • Appendix 2; Listing 2 |
| Revised grammar, spelling, etc. | Compliance with current company style guide and for general consistency. | Throughout protocol |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revisions to grammar, spelling, etc. | Compliance with current company style guide and for general consistency | • Throughout protocol |
| Revisions made per new company protocol template | Alignment with current Eisai template | • Synopsis –<br>  ○ Inclusion/Exclusion Criteria<br>• Section 9.1.2.3<br>• Section 9.3.1<br>• Section 9.3.2<br>• Section 9.5 (related subsections)<br>• Section 9.5.4<br>• Section 9.5.4.1<br>• Section 9.5.4.2<br>• Section 9.5.4.3 |
| Clarified classification of MCI due to AD | Clarification that MCI due to AD population will also be consistent with the research criteria for Prodromal AD in that impaired episodic memory is required and will be tested using a list learning task (the International Shopping List Task) | • Synopsis –<br>  ○ Study Design<br>• Section 9.1 |
| Replaced "enroll" with "randomize," pertaining to subject entry into study | Correction to terminology | • Synopsis –<br>  ○ Study Design<br>• Section 9.1<br>• Section 9.3 |
| Added criterion excluding subjects with hepatic impairment and total bilirubin greater than 1.5×ULN or INR greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded. | At request of FDA, exclude subjects who have hepatic impairment | • Synopsis –<br>  ○ Inclusion/Exclusion Criteria<br>• Abbreviation List<br>• Section 9.3.2 |
| Added coagulation parameters for prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR) to screening and baseline procedures | Screen for hepatic impairment | • Synopsis –<br>  ○ Inclusion/Exclusion Criteria<br>• Abbreviation list<br>• Section 9.3.2<br>• Table 4<br>• Table 6<br>• Table 8 |
| For subjects who discontinue study drug prematurely, conduct efficacy assessments postdose at same time points as subjects who continue in the study. Added FAQ to this set | To facilitate efficacy analyses, which are based on longitudinal modeling for all subjects | • Synopsis –<br>  ○ Study Design<br>• Section 9.1.2.2<br>• Section 9.3.3<br>• Section 9.5.4.1 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| of efficacy assessments. | | • Section 9.5.5<br>• Table 7 |
| Delete diagram of E2609 structure | This display is not needed for the protocol. The Investigator's Brochure has this information. | • Section 9.4.2.1 |
| Additional blood samples to be taken at Visits 19 and 20 | Samples are to be put in storage to allow for assessment of immune status at end of study, as needed. | • Synopsis –<br>○ Assessments<br>• Table 8 |
| Add subheadings to Section 9.7 describing the primary endpoint analysis, and text clarifying that no multiplicity adjustments will be done to account for the interim analyses | To distinguish clearly the primary analysis and the sensitivity analyses of the primary endpoint | • Synopsis –<br>○ Efficacy Analyses<br>• Section 9.7.1.6.1 |
| Clarification of PK sampling upon Early Discontinuation | Additional operational details of the timing of the PK sampling at the ED visit provided | • Section 9.5.1.4.1<br>• Table 7 |
| Clarification of ApoE testing | Clarification that the ApoE genetic testing will be for homozygous or heterozygous E4, versus non-E4 | • Section 9.5.1.4.2 |
| Revision to PK/PD interim analysis text | Confirm that interim PK/PD analysis will be conducted by an independent group | • Section 9.4.6 |
| Addition of text regarding safety signals with E2609 | To provide information on safety-driven dose adjustments | • Synopsis –<br>○ Study Design<br>• Section 9.1 |
| Addition of PBMC collection/assessment at Baseline, during treatment, and post-treatment | Recent animal studies have shown an effect of E2609 on this model so they will be added to the 202 clinical study as an additional exploratory assessment. | • Synopsis –<br>○ Safety Assessments<br>• Section 9.2.5<br>• Section 9.5.1.5<br>• Table 4<br>• Table 6<br>• Table 7<br>• Table 8 |
| Stipulate that exploratory biomarker analyses may be conducted using blood or CSF samples that may have been drawn for other purposes | To allow more flexibility for possible exploratory biomarker studies associated with study drug or disease, including miRNA and DNA | • Synopsis –<br>○ Assessments<br>• Abbreviation list<br>• Section 9.5.1.4.2<br>• Section 9.5.1.5.12<br>• Table 6<br>• Table 7 |
| Prohibit concomitant medications that are strong CYP3A4, inhibitors, but clarify that no restrictions are needed for other CYP3A4 | At request of FDA, in light of finding that inhibition of CYP3A4 by a reference agent increases plasma levels of E2609 | • Synopsis –<br>○ Concomitant Drug/Therapy<br>• Section 7.1 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| inhibitors, CYP3A4 inducers, or CES2 inhibitors | | • Section 9.4.7<br>• Appendix 2, Listing 6 |
| Addition of tests for viral characterization at Baseline | To confirm by serology information of subjects prior exposure to common viruses pre-dosing with study drug | • Section 9.5.1.2.2<br>• Table 4<br>• Table 6<br>• Table 8 |
| Use of a centralized dermatologist assessment via photography | A centralized approach, using standardized photography, to FDA-required serial dermatological assessments will be employed for consistency of assessments between sites and for consistency of longitudinal assessments of individual subjects. | • Synopsis –<br>○ Safety Assessments<br>• Section 9.2.5<br>• Section 9.5.1.5<br>• Section 9.5.1.5.8<br>• Table 6<br>• Table 7 |
| Removal of testing for benzodiazepines or opioids as part exclusion criteria #35 | To differentiate appropriate medicinal use from recreational drug use or abuse | • Synopsis –<br>○ Exclusion Criteria<br>• Section 9.3.2 |
| Addition of analysis of other covariates such as adjusted hippocampal volume will be studied | Hippocampal volume has been shown to correlate with rate of cognitive decline and as such is a key covariate to be used in the analyses. | • Synopsis –<br>○ Analysis of Primary Endpoint<br>• Section 9.7.1.6.1 |
| Addition of clarifications to ophthalmic examination | To provide more detail around the requirements for the ophthalmic exam | • Synopsis –<br>○ Safety Assessments<br>• Section 9.5.1.5.13<br>• Table 6<br>• Table 7 |
| Addition of details regarding specific method of CSF collection (ie, gravity drip) | Use of materials required for suction method when collecting CSF can affect the PD data and so it is important to make it clear that only the gravity drip method can be used for collecting CSF in this study for protecting the quality and the consistency of the CSF PD data. | • Section 9.5.1.3.3<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Addition of specific testing for B12 levels at Screening | Abnormally low serum vitamin B12 levels are exclusionary for the study (exclusion criterion 8) but a blood draw for Vitamin B12 was inadvertently missed out of Table 6 in protocol version 1. | • Synopsis –<br>○ Exclusion Criteria<br>• Section 9.3.2<br>• Section 9.5.1.2.3<br>• Figure 2<br>• Table 6 |
| Addition of details regard AEs that might be signals of possible drug abuse potential | Changed terminology re: collection of additional information for AEs that might be signals of possible abuse potential. No longer use the | • Synopsis –<br>○ Safety Assessments<br>• Section 9.2.5<br>• Section 9.5.1.5.1 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | word "narrative" in order to avoid potential confusion with standard clinical trial narratives eg, for serious adverse events, adverse events leading to withdrawal, etc. | • Appendix 4 |
| Addition of clarification regarding position for taking vital signs (ie, supine) | The American Heart Association guidelines only mention supine, standing, and sitting as positions for taking HR and BP measurements. Therefore, have changed required position from semi-supine to sitting. | • Section 9.5.1.5.4<br>• Table 6<br>• Table 7 |
| Stipulated that study drugs are to be taken with food | For consistency of treatment conditions | • Section 9.5.1.4.1 |
| Change to list of Study Specific AEs which should be considered SAEs | Eisai's standard procedures have changed such that non-serious study specific adverse events of interest are no longer reported to Eisai Product Safety; instead, any additional information required for such non-serious adverse events will be obtained through other methods. In addition, certain events (new onset seizures, ocular herpes) are now to be classified as serious as important medical events, regardless of whether they meet standard ICH serious criteria. | • Section 9.5.1.5.1<br>• Section 9.5.1.5.2 |
| Increased blood volume for PK | To match collection tubes and ensure sufficient sample for planned assays | • Table 8 |
| Corrected error in definition of PK analysis set | For accuracy | • Synopsis –<br>○ Study Endpoints<br>• Section 9.7.1.2 |
| Addition of details regarding discontinuation of study drug | To clearly and consistently differentiate "discontinuation from study drug" from "withdrawal from study" | • Synopsis<br>• Section 7<br>• Section 9.1.2.1<br>• Section 9.2.5<br>• Section 9.3.3<br>• Table 1<br>• Table 2<br>• Section 9.4.1<br>• Section 9.4.4<br>• Section 9.5.1.5.1<br>• Section 9.5.1.5.3<br>• Section 9.5.5 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Re-ordered prohibited medication lists | For consistency, all lists re-ordered in alphabetical order of generic drug name, and footnotes revised for overall consistency | • Appendix 2 |
| Moved nefazodone from Listing 9 to Listing 6 | Nefazodone is a strong CYP3A4 inhibitor and is therefore prohibited. | • Appendix 2 |

# 1 TITLE PAGE


## Clinical Study Protocol

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01 and 05) |
| **Sponsor:** | Eisai Inc.<br>100 Tice Boulevard<br>Woodcliff Lake,<br>New Jersey 07677<br>United States<br><br>Eisai Ltd.<br>European Knowledge Centre<br>Mosquito Way<br>Hatfield, Hertfordshire<br>AL10 9SN<br>United Kingdom<br><br>Eisai Co., Ltd.<br>4-6-10 Koishikawa<br>Bunkyo-Ku,<br>Tokyo 112 8088<br>Japan |
| **Investigational Product Name:** | Elenbecestat * (E2609)<br>* the proposed International Nonproprietary Name (pINN) (revised per Amendment 07) |
| **Indication:** | Alzheimer's disease |
| **Phase:** | 2 |
| **Approval Date:** | V1.0 15 Jul 2014 (original protocol)<br>V2.0 21 Oct 2014 (revised original protocol)<br>V3.0 28 May 2015 (Amendment 01)<br>V4.0 05 Nov 2015 (Amendment 02)<br>V5.0 06 Feb 2016 (Amendment 03)<br>V6.0 29 Jun 2016 (Amendment 04)<br>V7.0 26 Sep 2016 (Amendment 05)<br>V8.0 02 Nov 2016 (Amendment 06)<br>V9.0 01 Feb 2017 (Amendment 07) |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |
| **GCP Statement:** | This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities. |

**Confidentiality Statement:**

# 2 CLINICAL PROTOCOL SYNOPSIS

**Compound No.:**
E2609

**Name of Active Ingredient:**
*N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

**Study Protocol Title**
A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01and 05)

**Investigators**
Investigators in the United States only (revised per Amendment 05)

**Sites**
Approximately 35 sites, United States only (revised per Amendments 01, 02, 04, and 05)

**Study Period and Phase of Development** (revised per Amendment 07)

This Phase 2 study will include the following:

- Core Study: approximately 32 months including the Prerandomization and Randomization Phases (revised per Amendments 05 and 07)
- Open-label Extension (OLE) Phase: approximately 27 months including 24 months of treatment period and 3 months of off-treatment follow-up period (revised per Amendment 07)

**Objectives**

**Core Study** (revised per Amendment 07)

**Primary Objective** (revised per Amendment 05)

To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with elenbecestat (E2609) in Mild Cognitive Impairment (MCI)/Prodromal subjects and in subjects with Mild to Moderate Dementia due to Alzheimer's Disease (referred to as mild to moderate AD throughout the protocol) (revised per Amendments 01 and 07)

**Secondary Objectives** (revised per Amendments 02 and 05)

- To characterize the plasma and cerebrospinal fluid (CSF) pharmacokinetics (PK) of elenbecestat (E2609)

To assess the effects of elenbecestat (E2609) on Aβ(1-x) and Aβ(1-42) in CSF from 4 weeks and up to 18 months of treatment

**Exploratory Objectives**

(revised per Amendments 01, 02, 04, and 05)

- To explore the effects of elenbecestat (E2609) on CSF Aβ(1-40) and beta (β)-amyloid converting enzyme 1 (BACE1) measurements from 4 weeks and up to 18 months of

treatment

- To explore the effects of elenbecestat (E2609) compared with placebo on various biomarkers. Biomarkers to be explored may include but are not limited to:
    a. CSF biomarkers of neurodegeneration (eg, total tau [t-tau], phosphorylated-tau [p-tau]) after 18 months of treatment
    b. Plasma and CSF amyloid, and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment (revised per Amendment 06)
    c. Total hippocampal atrophy at 12 and 18 months of treatment, as measured by volumetric magnetic resonance imaging (vMRI)
    d. vMRI measurements including left and right hippocampal volume, whole brain volume and total ventricular volume at 6, 12, and 18 months of treatment
    e. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)
- To explore the effects of elenbecestat (E2609) compared with placebo on clinical status at various time points during 18 months of treatment, and during posttreatment follow-up, by assessment of:
    a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog$_{14}$)
    b. The Clinical Dementia Rating (CDR) scale
    c. The Mini-Mental State Examination (MMSE)
    d. The International Shopping List Task (ISLT)
    e. The CogState Brief Battery (CBB)
    f. The Functional Assessment Questionnaire (FAQ; also known as the Functional Activities Questionnaire)
- To explore the relationship between the treatment effects of elenbecestat (E2609) on measured clinical efficacy scales (eg, MMSE, CDR) and its effects on CSF amyloid, CSF amyloid isoforms, brain amyloid, and vMRI
- To explore relationships between both elenbecestat (E2609) dose and exposure, with pharmacodynamic (PD) and safety endpoints

**Open-Label Extension Phase** (revised per Amendment 07)

**Primary Objective:**

- To assess the long-term safety and tolerability of daily dosing with elenbecestat (E2609) 50 mg in MCI/Prodromal subjects and in subjects with Mild to Moderate Dementia due to AD

**Secondary Objectives**

- To explore the long-term effects of elenbecestat (E2609) on clinical status by assessment of:
    a. The MMSE
    b. The FAQ
- To explore the long-term effects of elenbecestat (E2609) on:
    a. vMRI including total hippocampal volume, left and right hippocampal volume, whole brain volume, and total ventricular volume with up to 24 months of treatment in the OLE Phase.

b. Plasma amyloid at 12 and 24 months of treatment in the OLE Phase.

**Study Design**

This will be a multicenter, placebo-controlled, double-blind, parallel-group, randomized, dose-finding study with an OLE Phase of up to 27 months in subjects with MCI/Prodromal AD or mild to moderate AD. (revised per Amendment 07) A common set of inclusion criteria, consistent with the National Institute on Aging–Alzheimer's Association (NIA-AA) clinical research criteria for MCI due to Alzheimer's Disease (AD) or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with the criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study consists of 3 phases: Prerandomization, Randomization, and OLE. The Prerandomization and Randomization Phases are referred to as the Core Study throughout the protocol. (revised per Amendment 07)

**Core Study**

The Prerandomization Phase (up to 60 days, plus an additional window of up to 30 days if required [revised per Amendment 02]) includes a Screening Visit (Visit 1) and a Baseline Visit (Visit 2). All screening assessments (within 4 distinct tiers) must be completed, and eligibility to continue in the study confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

The study will be limited to approximately 35 sites in the United States. (revised per Amendments 01, 02, and 04) Subjects will initially be randomized 1:1:1:1 to 4 treatment groups (5, 15, or 50 mg elenbecestat [E2609] or placebo) within each of the 2 clinical populations. (revised per Amendments 01, 04, 05, and 06) In addition to the placebo group, 3 elenbecestat (E2609) doses will be used to reduce CSF amyloid β levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/pharmacodynamic (PD) modeling has shown that these doses should achieve these targets when administered once daily (QD) with food, and these doses will be evaluated based on the 4-week (or later) assessment of CSF Aβ(1-x) from subjects who provide voluntary consent for CSF measurement. (revised per Amendment 02) Upon implementation of Amendment 06, at the next regularly scheduled visit, subjects receiving elenbecestat (E2609) 5 or 15 mg who have not yet completed Visit 17 (Week 66), will be re-assigned in a blinded manner to elenbecestat (E2609) 50 mg for the remainder of the double-blind treatment period. In order to maintain the blind, all subjects who have not yet had Visit 17 will go through the same procedures with the placebo-randomized subjects continuing to receive placebo and those randomized to elenbecestat (E2609) 50 mg continuing to receive 50 mg. (revised per Amendment 06)

Safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the 1st subject is randomized into the study through the time the last subject is randomized, an independent data safety monitoring board (DSMB; including at least 1 immunologist) will review all safety data in an unblinded manner. (revised per Amendment 06) The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. (revised per Amendments 01, 04, and 05)

Interim analyses of the elenbecestat (E2609) plasma PK for all subjects and the elenbecestat (E2609)

CSF PK and PD profiles will be performed on baseline data and samples collected after at least 4 weeks of treatment. (revised per Amendment 05) These interim analyses, as well as analyses of safety data, will be performed on an ongoing basis throughout the study. Refer to the Interim Analysis section for more detail. These data will be used to evaluate the CSF PD effects of elenbecestat (E2609) doses, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels. (revised per Amendments 01 and 02) The median and mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks or more of treatment for each dose of elenbecestat (E2609) and the 90% confidence interval (CI) for the median will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data and will relate the average steady state plasma concentration of elenbecestat (E2609) to CSF Aβ(1-x) percentage reduction from baseline determined after at least 4 weeks of dosing. (revised per Amendments 01, 02, 03, 04, and 05)

Once subjects have completed at least 12 weeks of treatment (or discontinued study drug early) an interim safety analysis will be conducted by Eisai and the DSMB. At the completion of this interim safety review, the frequency of subsequent unblinded safety reviews will be re-evaluated by the DSMB and the Sponsor and this information will be provided in the DSMB charter. (revised per Amendment 06) Subjects will continue study drug while the DSMB reviews all the available safety data. (revised per Amendments 01, 04, 05, and 6).

**Open-Label Extension Phase** (revised per Amendment 07)

The OLE Phase allows eligible subjects to receive elenbecestat (E2609) 50 mg daily for up to 24 months (2 years).

All subjects who complete 18 months of treatment and 12 weeks of follow-up in the Core Study and who satisfy the entry criteria for the OLE Phase are eligible to enter the OLE Phase. After completing all Visit 20 procedures in the Core Study Follow-up Period, eligible subjects will have the option to participate in the OLE Phase within 4 weeks of Visit 20 of the Core Study. These subjects may transition to the OLE Phase immediately following Visit 20 (on the same day) if the decision to proceed with the OLE Phase has been made at that time. The Medical Monitor must be contacted if Visit 21 is to occur more than 4 weeks after Visit 20.

For all subjects, assessments performed at Visit 20 may serve as Visit 21 (start of the OLE Phase) results with the following exceptions: laboratory assessments and vital signs must be repeated if Visit 21 occurs more than 10 days from Visit 20.

Subjects who are eligible and who consent to participate in the OLE Phase will be administered elenbecestat (E2609) 50 mg daily at Visit 21. Subjects with pending INR and serum pregnancy test results (females subjects of child bearing potential only) but who are otherwise eligible may begin OLE dosing at Visit 21; however, these subjects must discontinue study drug treatment immediately if either test result meet the exclusion criteria.

During the OLE Phase, safety assessments will continue to be monitored and all AEs and SAEs will be recorded. Vital signs, hematology, blood chemistry, and urine values will be monitored at every scheduled visit. Clinical assessments (MMSE and FAQ) will be administered every 3 months. Blood for PD analyses will be collected every 12 months. All subjects will be assessed using safety MRIs and vMRI measurements at the end of the OLE Phase.

**Early Discontinuation (Core Study)**

Subjects who prematurely discontinue taking study drug prematurely for any reason during the Core

Study will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug. (revised per Amendments 04 and 05)

**Follow-Up (Core Study)**

All subjects, regardless of whether they complete all 18 months of treatment or prematurely discontinue study drug, will complete 4 post-treatment Follow-Up Visits: 2, 4, 8, and 12 weeks after the last dose of study drug. If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the post-treatment Follow-up Period. (revised per Amendment 04)

**Early Discontinuation** (**Open-Label Extension Phase)** (revised per Amendment 07)

Subjects who prematurely discontinue study drug for any reason during the OLE Phase will undergo an ED Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug.

**Follow-Up (Open-Label Extension Phase)** (revised per Amendment 07)

All subjects, regardless of whether they complete all 24 months of treatment in the OLE Phase or prematurely discontinue study drug, will complete 2 posttreatment Follow-Up Visits at 4 and 12 weeks after the last dose of study drug. (revised per Amendment 07) If clinically indicated, more frequent safety assessments can be conducted as part of Unscheduled Visits during the OLE Follow-up Period.

**Number of Subjects**

Approximately 400 MCI/Prodromal or mild to moderate AD subjects will be screened to provide approximately 60 (±20%) randomized subjects (with a target of approximately 15 subjects per treatment arm). There will be no limit to the number of subjects randomized from either clinical cohort. (revised per Amendments 01, 02, 04, and 05)

**Inclusion Criteria**

**Core Study**

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD or AD dementia and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at Screening Visit 1:**
(revised per Amendment 02)

a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation
b. Cognitive impairment of at least 1 standard deviation (SD) from age adjusted norms in delayed recall on the ISLT. Alternatively, cognitive impairment of at least 0.5 SD from age-adjusted norms in delayed recall on the ISLT plus impairment of at least 1 SD from age-adjusted norms in at least 1 other computerized learning and memory test (ISLT immediate recall, or 1 of the learning and memory components of the CBB). (revised per Amendment 02)
c. FAQ ≤24 (revised per Amendment 01)
d. MMSE ≥16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading; an historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group (revised per Amendment 02)
3. Male or female, age 50 to 85 years, inclusive at time of consent
4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.
5. If receiving acetylcholinesterase inhibitors (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.
6. Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization.

**Open-Label Extension Phase** (revised per Amendment 07)

1. Subjects who complete the 18-month treatment and the 12-week follow-up period (Visit 20) in the Core Study and whose Visit 20 falls within a 4-week window from the start of the OLE Phase (Visit 21). Permission must be obtained from the Medical Monitor if Visit 21 is to occur more than 4 weeks from Visit 20.
2. Subjects must continue to have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the OLE Phase.

**Exclusion Criteria (revised per Amendment 04)**

**Core Study**

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or magnetic resonance imaging (MRI)
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.

5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and <1 cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could, in the opinion of the investigator, confound the MCI/Prodromal or mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendments 01 and 02)
7. A score of ≥8 on the 15-item Geriatric Depression Scale at Screening
8. Abnormally low serum vitamin B12 (< lower limit of normal [LLN]) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the lower limit of normal (LLN) for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
12. Any contraindications to lumbar puncture (LP) for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity). Only applicable to subjects consenting to CSF sample collection (revised per Amendment 02)
13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization

20. Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below population-adjusted LLN at Screening or Baseline and confirmed by a repeat test conducted 1 week after the initial test. The population-adjusted LLN for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are 396, 157, and 74 cells/μL respectively. (revised per Amendment 02)
23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the Investigator and the Medical Monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of clinical immunodeficiency. The discussion with the Medical Monitor should include a detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)
24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate electrocardiograms (ECGs). A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute at Screening or Baseline
29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy;

these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.

33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo). Diagnosis of an underlying disease causing hypopigmentation is not necessary for exclusion if the clinical presentation is consistent with such a condition. Hypopigmentation associated with scarring need not be exclusionary. (revised per Amendment 02)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the 1st dose of study drug.
43. Females of childbearing potential who:
    a. Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period and for

28 days after study drug discontinuation.

b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.

c. Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
(NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

**Open-Label Extension Phase** (revised per Amendment 07)

1. Subjects who discontinue study drug prematurely during the Core Study are not eligible to participate in the OLE Phase.
2. Subjects with any active infection within 4 weeks of Visit 21.
3. Subjects with absolute lymphocyte count below the LLN within 10 days of Visit 21.
4. Subjects who develop the following conditions from the time of screening for the Core Study to the start of the OLE Phase:

    a. Hepatic impairment, with total bilirubin greater than 1.5 × ULN or INR greater than 1.7. Subjects with Gilbert's syndrome need not be excluded on the basis of an elevated bilirubin, provided that they have no other signs or symptoms suggestive of hepatic impairment

    b. Any contraindications to MRI scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners)

    c. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately

    d. Immunoglobulin (Ig) deficiency or other immunodeficiency disorders

    e. Chronic viral hepatitis

    f. TB

    g. Ophthalmic shingles

    h. Ocular HSV infection

    i. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:

        - Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded
        - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded
        - Cutaneous manifestations of immunological disease that do not require systemic

immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted)

j. Malignant neoplasms (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject from OLE).

5. Subjects with prolonged QTcF interval at Visit 20 or Visit 21. Subjects with a single 12-lead ECG QTcF >450 msec should have 2 additional ECGs performed at least 1 min apart and the mean QTcF from the triplicate ECGs should be calculated. Subjects with a mean QTcF value >450 msec are not eligible to enter the OLE Phase.
6. Subjects with significant pathological findings on brain MRI including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).
7. Subjects who have a "yes" answer to the C-SSRS suicidal ideation questions 4 or 5 at Visit 20 or Visit 21 or any suicidal behavior during the study prior to the start of the OLE Phase.
8. Female subjects of child bearing potential who meet any of the follow criteria:
    a. Do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period and for 28 days after study drug discontinuation
    b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation
    c. Who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
9. Females who are lactating or pregnant (as documented by a positive β-hCG or hCG test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Visit 20 or Visit 21.
10. Subjects with medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments.
11. Any other clinically significant abnormal findings in vital signs, ECGs and laboratory tests that would, in the investigator's opinion, would affect the subject's safety or interfere with study assessments during the OLE Phase.

**Study Treatments (Core Study)**

Elenbecestat (E2609) tablets of 5-, 10-, and 25-mg dose strengths will be supplied. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 2 tablets, which when combined will make up the required doses of elenbecestat (E2609) or placebo, to be administered orally QD with food. (revised per Amendment 05)

**Study Treatments (OLE Phase)** (revised per Amendment 07)

Elenbecestat (E2609) tablets of 50-mg dose strengths will be supplied during the OLE. Each subject

will take 1 tablet orally QD, with food.

**Duration of Treatment**

**Core Study**

The maximum duration of a subject's participation in the study will be approximately 2 years, comprising the following:

- Screening and Baseline Periods (Prerandomization Phase): up to 60 days, plus an additional window of up to 30 days if required (revised per Amendment 02)

  (In subjects who have an active infection within 4 weeks of the planned randomization date, the duration of the pre-randomization phase can be extended by up to 4 weeks to allow additional time for resolution of the infection.)
- Treatment Period (Randomization Phase): up to 78 weeks
- Follow-up Period (Randomization Phase): 12 weeks (post last dose)

**Open-Label Extension Phase** (revised per Amendment 07)

The duration of the OLE Phase will be approximately 116 weeks, comprising the following:

- Treatment Period: up to 104 weeks (24 months)
- Follow-up Period: 12 weeks (after the last dose)

**Concomitant Drug/Therapy (Core Study and Open-label Extension Phase)** (revised per Amendments 04 and 07)

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit in the Core Study (for subjects participating in the Core Study only) or the last treatment visit in the OLE Phase (for subjects participating in the OLE Phase) (see Appendix 2 for a detailed listing of these agents) (revised per Amendment 07):

- Drugs that may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization. However, during the treatment period of the study, short term (not more than 14 days) use of steroids up to the equivalent of prednisolone 40 mg QD is permitted after discussion with the Medical Monitor. Dosing with study drug should be suspended from the time steroid treatment is started. Complete blood count and lymphocyte subsets should be determined prior to starting steroid treatment and continue to be monitored weekly. Study drug may be resumed after discussion with the Medical Monitor when the following conditions are met: (1) treatment with steroids has been completed for at least 1 week; (2) absolute lymphocytes not <LLN; (3) no lymphocyte subsets are below the discontinuation threshold (for Core Study only); (4) the investigator considers that the medical condition which required treatment with steroids has improved or resolved. Weekly testing of lymphocyte subset counts (for Core Study only) and CBC with differentials (for Core Study and

OLE) is required for 4 weeks following resumption of study drug administration. (revised per Amendment 04)

- (revised per Amendment 06)

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for any efficacy analyses. (revised per Amendment 05)

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed. Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before randomization. They may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 04)
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if, in the opinion of the investigator, this will not interfere with study procedures or subject safety, and are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks

Antiplatelet therapy: (revised per Amendment 04)

- For subjects who consent to CSF sample collection: Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) are permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.
- For subjects who do not consent to CSF sample collection: Aspirin and clopidogrel, individually or in combination, are permitted.

**Assessments**

**Efficacy Assessments (Core Study)**

Alzheimer's Disease Assessment Scale - cognitive subscale: The 14-item version will be used since it is considered more relevant for subjects with MCI/Prodromal AD or mild AD.

Clinical Dementia Rating: Assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

Mini-Mental State Examination: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing.

International Shopping List Task: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall.

CogState Brief Battery: A computer-based battery comprising 4 cognitive tests:

- Detection – a simple reaction time test. Speed of response is the measure.
- Identification – a simple choice reaction time test. Speed of response is the measure.
- One Card Back – a simple working memory test. Accuracy of response is the measure.
- One Card Learning – a visual learning and memory test. Accuracy of response is the measure.

Functional Assessment Questionnaire: The FAQ has 10 items concerned with performing daily tasks necessary for independent living. The caregiver or informant provides performance ratings on 10 complex activities of daily living performed within the preceding 4 weeks. (revised per Amendment 04)

Volumetric Magnetic Resonance Imaging: vMRI will be used to evaluate disease modification, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs.

**Pharmacokinetic Assessments (Core Study)**

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609). For subjects who consent to CSF sample collection, CSF samples will be collected for the determination of elenbecestat (E2609) concentrations. (revised per Amendment 02) Analyses of metabolite concentrations may be performed depending on emerging data from other studies with elenbecestat (E2609).

**Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments (Core Study)**

Brain atrophy will be measured by vMRI: see Efficacy Assessments (above).

The soluble biomarkers Aβ(1-x), Aβ(1-42), (Aβ(1-40), total tau (t-tau), and p-tau will be measured in subjects who consent to CSF sample collection (revised per Amendment 02). BACE1 levels and activity in CSF will also be measured in subjects who consent to CSF sample collection (revised per Amendment 02). Other exploratory biomarkers and amyloid isoforms (eg, Aβ[1-40]) may also be evaluated in plasma or CSF. (revised per Amendment 04) Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

Amyloid PET imaging will be used to confirm that all subjects eligible for progression to the Baseline Period have amyloid deposition in the brain. An historical amyloid positive PET scan may be used, if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02) Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses. (revised per Amendments 02 and 05)

Apolipoprotein E (*ApoE*) and N-acetyltransferase 2 (*NAT2)* genotyping/phenotyping will be conducted. *ApoE4* homozygous or heterozygous status versus non-carriers and *NAT2* status will be used in the statistical analysis to determine the effects on treatment response and safety. Remaining genomic DNA may also be stored for up to 15 years to be used to examine the role of DNA sequence variability on the absorption, distribution, metabolism, and elimination of elenbecestat (E2609), development of adverse events (AEs), as well as the underlying AD. Variations in elenbecestat (E2609) exposure or the occurrence of AEs observed in the study population may be evaluated by

correlation of single-nucleotide polymorphisms with PK, safety, or PD data.

**Safety Assessments (Core Study)**

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR. (revised per Amendment 01) Routine safety assessments will include the monitoring and recording all AEs and serious adverse events (SAEs), monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

Complete blood counts and lymphocyte subset absolute counts and percentages will be measured (by a centralized laboratory) every week for the 1st month, every 2 weeks for the next 2 months (Months 2 and 3) and monthly for the next 3 months (Months 4, 5, and 6). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at all 4 Follow-Up Visits at 2, 4, 8, and 12 weeks after the last dose of study drug. Serum IgG, IgA, and IgM will be monitored monthly for the 1st 3 months, at 6, 12, and 18 months, and at the Follow-Up Visits that occur 4, 8, and 12 weeks after the last dose of study drug. (revised per Amendment 04)

Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and posttreatment for exploratory immunomodulatory and immune-based analyses.

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at baseline and at 3-month intervals during the Treatment Period. These assessments will specifically include evaluation of any areas of depigmentation or rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregivers/ informants will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so such AEs can be reviewed promptly.

Baseline and on-study blood and DNA samples will be taken and stored for all subjects, and CSF samples will be taken and stored for all subjects from whom CSF samples were collected (revised per Amendments 02 and 04). These samples may be tested for exploratory biomarkers associated with study drug or disease, or in the event that a subject develops AEs that warrant further investigation (eg, to test if a subject with a treatment-emergent infection was exposed to any suspected infective agents before treatment with study drug).

Safety brain MRI assessments will be performed at Screening, at 6, 12, and 18 months during the Treatment Period and at the final Follow-Up Visit. Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Full neurologic examinations will be performed at Baseline, at 6, 12, and 18 months, and at the 4- and 12-week Follow-Up Visits, by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. The neurologic examinations will include muscle strength testing and assessment of cranial nerves including olfaction, with the use of the Brief Smell Identification Test, as well as other parts of the CNS. (revised per Amendment 04)

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments will include the ADAS-$cog_{14}$, MMSE, and CBB.

An assessment of suicidality using the C-SSRS will be performed at Screening and Baseline and at

regular intervals throughout the Treatment and Follow-up Periods.

An ophthalmic examination (including retinal examination) will be conducted at Baseline. An additional examination will be conducted if the subject experiences visual disturbances during the course of the study.

A number of safety-related criteria for discontinuation of study drug are specified for the study.

**Efficacy Assessments (Open-Label Extension Phase)** (revised per Amendment 07)

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing.

FAQ: The FAQ has 10 items concerned with performing daily tasks necessary for independent living. The caregiver or informant provides performance ratings on 10 complex activities of daily living performed within the preceding 4 weeks.

vMRI: vMRI will be used to evaluate disease modification, including the changes from the Core Study Baseline and the OLE Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs.

**Pharmacodynamic and Other Biomarker Assessments (Open-Label Extension Phase)** (revised per Amendment 07)

Exploratory biomarkers and amyloid isoforms (eg, Aβ[1-40]) will be evaluated in plasma.

**Safety Assessments (Open-Label Extension Phase)** (revised per Amendment 07)

All subjects will be assessed for their eligibility to for OLE Phase at Visit 21. Where applicable, results of the safety assessments (including laboratory assessment, physical examination, and neurologic examination) conducted during Visit 20 will serve as Visit 21 values for the OLE Phase with the following exceptions: if Visit 21 occurs more than 10 days after Visit 20, all laboratory safety assessments and vital signs must be repeated.

Routine safety assessments will include the monitoring and recording all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, and physical, dermatologic and neurologic examinations at regular intervals.

There will be no centralized dermatological assessments in the OLE Phase. Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly.

Full neurologic examinations will be performed at the start of the OLE Phase (Visit 20 or 21) and at every 6 months during the OLE treatment period. An additional neurologic examination will also be performed at the final Follow-Up Visit. The neurologic examinations will include muscle strength testing and assessment of cranial nerves including olfaction, with the use of the Brief Smell Identification Test, as well as other parts of the CNS.

Complete blood counts and percentages will be measured (by a centralized laboratory) every scheduled visit. Lymphocyte subset absolute counts and percentages will also be measured (by a central laboratory) and the results will be reviewed by the Sponsor and the members of the DSMB only.

PBMCs will be collected every scheduled visit and posttreatment for exploratory immunomodulatory

and immune-based analyses. Additional blood samples will be collected and stored; these samples may be used for further exploratory biomarker analyses, and/or, in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

Safety brain MRI and vMRI assessments will be performed at the end of the OLE treatment period (Visit 32 or ED Visit). Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Assessment of suicidality using the C-SSRS at the start of the OLE Phase (Visit 21), at the end of OLE treatment (Visit 32 or ED Visit), and at the end of the OLE Phase (Visit 34). Clinical assessment of suicidality will be performed at every visit scheduled interim safety visit during the OLE Phase.

**Bioanalytical Methods**

Plasma and CSF elenbecestat (E2609) concentrations will be measured by a validated liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) in both CSF and plasma will be measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendment 04)

BACE1 levels and activity may be measured using a customized assay. Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

**Statistical Methods**

All statistical tests will be based on the 5% (2-sided) level of significance. (revised per Amendment 05)

**Study Endpoints (Core Study)**

**Primary Endpoint**

- Safety and tolerability, which include incidence of treatment-emergent adverse events (TEAEs) and SAEs, laboratory parameters, vital signs, and ECG parameters (revised per Amendment 05)

**Secondary Endpoints**

(revised per Amendments 02 and 05)

- % reduction of Aβ(1-x) and Aβ(1-42) in CSF relative to baseline after at least 4 weeks and 18 months of treatment
- The population PK parameters of elenbecestat (E2609) in CSF and plasma, including the effect of intrinsic and extrinsic factors (including NAT2 phenotype)

**Exploratory Endpoints**

(revised per Amendments 01, 02, 04, and 05)

Change from baseline in:

- CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to

18 months of treatment

- CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- CSF amyloid and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment (revised per Amendment 06)
- Total hippocampal volume at 12 and 18 months of treatment as measured by vMRI
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months as measured by vMRI
- Amyloid PET standardized uptake value ratio (SUVR) composite at 18 months for brain amyloid levels
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog$_{14}$, CDR, MMSE, ISLT, CBB, and FAQ

**Study Endpoints (Open-label Extension Phase)** (revised per Amendment 07)

**Primary Endpoint**

- Safety endpoints: AE, vital sign, ECG, physical examination, clinical laboratory test, any relevant test of cognitive function to evaluate decline, and MRI parameters (microhemorrhage, vasogenic edema, and other clinically significant abnormalities).

**Secondary Endpoints**

Changes from Core Study and OLE baselines in:

- MMSE and FAQ at each visit assessed in the OLE Phase
- Plasma amyloid measurements at 12 and 24 months of OLE treatment
- Total hippocampal volume, left and right hippocampal volume, whole brain volume, and total ventricular volume with up to 24 months of OLE treatment as measured by vMRI

**Analysis Sets (Core Study)**

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose exploratory efficacy measurement. (revised per Amendment 05)
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

**Analysis Sets (Open-label Extension Phase)** (revised per Amendment 07)

- The OLE Safety Analysis Set (OLE-SAS) is the group of subjects who receive at least 1 dose of study drug during the OLE Phase.
- The OLE Full Analysis Set (OLE-FAS) is the group of subjects who receive at least 1 dose of study drug during the OLE Phase and have at least 1 postdose efficacy assessment during the OLE Phase.
- The OLE PD Analysis Set is the group of subjects who have at least 1 posttreatment PD

measurement during the OLE Phase.

**Efficacy and Biomarker Analyses** (revised per Amendment 05)

**Analysis for the Primary Endpoint (Core Study)**

There is no primary efficacy endpoint. (revised per Amendment 05)

**Analysis for the Secondary Endpoints (Core Study)**

An mixed-effects model with repeated measures (MMRM) will be used to analyze the following secondary endpoint:

Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) from 4 weeks and up to 18 months. Data from early discontinuations will also be included. (revised per Amendment 05)

**Analysis for Exploratory Endpoints (Core Study)**

(revised per Amendments 01, 02, 04, and 05)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months of treatment
- Change from baseline in CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Change from baseline in plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- Change from baseline in CSF amyloid and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment (revised per Amendment 06)
- Change from baseline in total hippocampal atrophy at 12 and 18 months as measured by vMRI
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months as measured by vMRI
- Change from baseline in Amyloid PET SUVR composite at 18 months for brain amyloid levels

The following efficacy endpoints will be summarized using descriptive statistics:

- Change from baseline in the clinical assessments: ADAS-cog$_{14}$, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months

The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

**Pharmacokinetic Analyses (Core Study)**

The PK Analysis Set will be used for elenbecestat (E2609) concentration listings and for summaries of elenbecestat (E2609) concentrations in plasma and CSF by dose and day. elenbecestat (E2609) metabolite PK data may also be listed and summarized. (revised per Amendment 05)

A population PK approach will be used to characterize the plasma PK of elenbecestat (E2609). For this approach, plasma PK data from this study will be pooled with relevant data from Phase 1 studies. As appropriate, the effect of covariates on the PK of elenbecestat (E2609) will be evaluated. The PK model will be parameterized for oral clearance (CL/F) and apparent volume of distribution (Vz/F) for elenbecestat (E2609). Derived exposure parameters such as steady state area under the concentration time curve ($AUC_{ss}$) and average concentration ($C_{avg}$) of elenbecestat (E2609) and other derived parameters will be calculated from the model using the individual estimates parameterized for oral

clearance and dosing history. (revised per Amendment 04)

**Pharmacodynamic Analyses (Core Study)**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). The percentage change from baseline in CSF Aβ(1-x), Aβ(1-40), Aβ(1-42), t-tau, p-tau, and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months will be analyzed and presented graphically. (revised per Amendments 04 and 05) Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status. Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses (Core Study)**

The PK/PD relationship between CSF biomarker levels, amyloid load on PET, vMRI and elenbecestat (E2609) dose, plasma and CSF exposure will be initially explored graphically and any emergent relationship will be explored through population PK/PD modeling. Additionally, the relationship between CSF exposure to elenbecestat (E2609) and the change from baseline for 18 months in the ADAS-cog, the CDR, and the MMSE will be explored graphically. (revised per Amendments 04 and 05)

Additionally, the relationship between plasma exposures of elenbecestat (E2609) and select lymphocyte parameters will be explored graphically, and any emergent relationship will be explored using population-based modeling methods. (revised per Amendment 04)

**Pharmacogenomic Analyses (Core Study)**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. Further information is in the "Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments" section. Details of pharmacogenomic testing may be provided and reported separately.

**Safety Analyses (Core Study)**

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements, and cognitive decline assessment such as CBB will be summarized by treatment group using descriptive statistics. (revised per Amendment 05)

<u>Lymphocyte Subsets</u>

Lymphocyte subsets, including but not limited to, CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages]) and regulatory T cells will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose.

Serum IgG, IgM, IgA will be measured and summarized in the same manner as other laboratory parameters. (revised per Amendment 04)

**Interim Analyses Core Study**

In order to make decisions about the remainder of the study as well as the full elenbecestat (E2609) clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. Investigators, other clinical site staff, subjects, caregivers/informants and study team will remain blinded to study treatment. (revised per Amendments 03 and 05)

An interim safety analysis will also be conducted when 60 subjects (±20%) have completed 12 weeks of treatment (or discontinue study drug early). (revised per Amendments 01, 03, 04, and 05)

**Stratification Core Study**

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

**Efficacy Analyses (Open-label Extension Phase)** (revised per Amendment 07)

The following secondary efficacy endpoints will be summarized by descriptive statistics and/or graphs, using OLE-FAS:

- Changes from Core Study and OLE baselines in MMSE and FAQ scores
- Changes from Core Study and OLE baselines in total hippocampal volume, left and right hippocampal volume, whole brain volume, and total ventricular volume at up to 24 months as measured by vMRI

The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

**Pharmacodynamic Analyses (Open-label Extension Phase)** (revised per Amendment 07)

The OLE PD Analysis Set will be used for the summaries and analyses of PD biomarkers. The percentage change in plasma amyloid measurements from Core Study and OLE baselines to 12 and 24 months of OLE treatment will be analyzed and presented graphically.

**Safety Analyses (Open-label Extension Phase)** (revised per Amendment 07)

Safety analysis will be performed similarly to the Core Study. Evaluations of safety will be performed on the OLE Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and changes from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements, and cognitive decline assessment such as MMSE will be summarized by using descriptive statistics.

**Sample Size Rationale**

A total of 15 subjects per dose is deemed sufficient to derive adequate safety and PK/PD data to aid in the selection of appropriate doses and the design of the Phase 3 studies that may be planned subsequently. (revised per Amendment 04) Based upon the selection of the elenbecestat (E2609) 50-mg dose for the Phase 3 studies, subjects randomized to the active treatment arms will be re-assigned to the selected 50-mg dose for further evaluation. (revised per Amendment 06)

# 3 TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES



## LIST OF IN-TEXT FIGURES



## LIST OF APPENDICES

# 4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| Aβ | amyloid β |
| Aβ(1-x) | amyloid β (1-x) (ie, the amyloid β monomer from amino acid 1 to x [eg, 1-42]) |
| AChEI | Acetylcholinesterase inhibitor |
| AD | Alzheimer's disease |
| ADAS-cog | Alzheimer's Disease Assessment Scale - cognitive subscale |
| AE | Adverse Event |
| ApoE | Apolipoprotein E |
| AUC | area under the concentration × time curve |
| $AUC_{(0\text{-}24h)ss}$ | area under the concentration × time curve at steady state from time zero to 24 hours |
| $AUC_{ss}$ | steady state area under the concentration × time curve |
| BACE1 | Beta (β)-amyloid converting enzyme 1 |
| BP | blood pressure |
| bpm | beats per minute |
| $C_{avg}$ | average concentration |
| CBB | CogState Brief Battery |
| CBC | complete blood count |
| CBP | childbearing potential |
| CDR | Clinical Dementia Rating |
| CES2 | carboxyesterase-2 |
| CFR | Code of Federal Regulations |
| CL/F | oral clearance |
| $C_{max,ss}$ | maximum plasma concentration at steady state |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| CI | confidence interval |
| CRA | clinical research associate |
| CRF | case report form |
| CRO | contract research organization |
| CSF | cerebrospinal fluid |
| $C_{ss,av}$ | average steady-state concentration |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CTA | Clinical Trial Agreement |
| CYP | cytochrome P450 |

| Abbreviation | Term |
|---|---|
| DSMB | data safety monitoring board |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| ED | early discontinuation |
| ELISA | enzyme-linked immunosorbent assay |
| FAQ | Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire) |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FLAIR | fluid-attenuated inversion recovery |
| GCP | Good Clinical Practice |
| GDS | Geriatric Depression Scale |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |
| HCVAb | hepatitis C virus antibody |
| HSV | herpes simplex virus |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ID | identifier |
| IEC | Independent Ethics Committee |
| Ig | immunoglobulin (eg, IgA, IgG, IgM) |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISLT | International Shopping List Task |
| IxRS | interactive voice and web response system |
| LLN | lower limit of normal |
| LNH | low/normal/high |
| LP | lumbar puncture |
| MAD | multiple ascending dose |
| MCI | mild cognitive impairment |
| MCI/Prodromal | Mild Cognitive Impairment due to Alzheimer's Disease/ Prodromal Alzheimer's Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mild to moderate AD | mild to moderate dementia due to Alzheimer's Disease |
| miRNA | micro-ribonucleic acid |

| Abbreviation | Term |
|---|---|
| MMRM | mixed-effects model with repeated measures |
| MMSE | Mini-Mental State Examination |
| MRI | magnetic resonance imaging |
| NAT2 | N-acetyltransferase 2 |
| NIA-AA | National Institute on Aging-Alzheimer's Association |
| OLE | Open-label Extension |
| PBMC | peripheral blood mononuclear cell |
| PD | Pharmacodynamic(s) |
| PET | positron emission tomography |
| PGx | pharmacogenomic(s) |
| pINN | proposed International Nonproprietary Name |
| PK | pharmacokinetic(s) |
| PRN | Pro re nata |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| p-tau | phosphorylated-tau |
| QD | once daily |
| QTc | corrected QT interval |
| QTcF | QTc interval calculated using Fridericia's formula |
| R | Randomization |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reaction |
| SUVR | standardized uptake value ratio |
| TB | Tuberculosis |
| TEAE | treatment-emergent adverse event |
| TEMAV | treatment-emergent markedly abnormal laboratory values |
| t-tau | total tau |
| ULN | upper limit of normal |
| UNS | Unscheduled |
| vMRI | volumetric magnetic resonance imaging |
| Vz/F | apparent volume of distribution |
| WHO DD | World Health Organization Drug Dictionary |
| β-hCG | beta-human chorionic gonadotropin |

# 5 ETHICS

## 5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA][s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigators or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

## 5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (CFR) (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

- European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved European Union member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

## 5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject and the identified caregiver or informant, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or understand it or if the identified caregiver or informant is unable to read, an impartial witness should be present during the entire informed consent discussion. If, in the Investigator's opinion, a subject lacks capacity to consent, the subject's assent should be obtained in addition to the written informed consent of a legal representative (capacity to consent and definition of legal representative should be determined in accordance with applicable local laws and regulations). (revised per Amendment 01) After the ICF and any other written information to be provided to subjects is read and explained to the subject and the identified caregiver or informant, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified caregiver or informant should also consent to supporting the subject's participation in the study and will be provided with a separate written ICF for his or her participation in the study, to be signed before he or she participates in any further aspects of the study.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified caregiver or informant must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified caregiver or informant will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified caregiver or informant should be

informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

All subjects will also be asked to provide written consent for cerebrospinal fluid (CSF) sampling at Baseline and after receiving study drug for from 4 weeks and up to 18 months (or at Early Discontinuation). This consent for CSF sample collection is not required for study eligibility. (revised per Amendments 02 and 05)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects and will be via a separate, optional CSF consent form for the study. (revised per Amendment 04)

# 6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 35 investigational sites in the United States. (revised per Amendments 01, 02, 04, and 05)

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

# 7 INTRODUCTION

At this time, there is no cure for Alzheimer's disease (AD), no known way of slowing down the progression of this disease, and no approved treatment available to reverse the deterioration. There is, therefore, an urgent unmet medical need for drugs that slow or prevent disease progression. Beta-amyloid converting enzyme 1 (BACE1) is a key enzyme responsible for the production of amyloid β (Aβ) peptides and plaque formation, and several reports have described elevated levels of BACE1 in AD brains (Coulson, et al., 2010; Lu, et al., 2012). Once amyloid plaques form, Aβ causes BACE1 levels to increase further, thus accelerating Aβ generation and plaque growth via a positive feedback loop. Therefore, BACE1 is a promising target for modifying or treating AD.

It is now widely accepted that mild cognitive impairment (MCI) due to AD and mild to moderate AD dementia are stages on a single disease spectrum, which follows an Alzheimer's pathological cascade. (revised per Amendment 01) Recent consensus papers from the international workgroups of the National Institute on Aging-Alzheimer's Association (NIA-AA), have endorsed this hypothesis (Albert, et al., 2011; Jack, et al., 2011; McKhann, et al., 2011; Rosen, et al., 1984; Sperling, et al., 2011).

From a clinical standpoint, demonstration of an effect on slowing disease course is hampered by the lack of sensitive tools for detecting relatively small changes in progression or treatment effect especially in early disease. In addition, drugs that are expected to slow disease progression require longer study durations to ensure adequate separation from placebo. These challenges have resulted in the use of biomarkers as surrogates for clinical effect in Phase 2 studies, in order to facilitate the development process for disease modifying agents. However, subsequent Phase 3 AD studies based solely on biomarker findings in Phase 2 have failed to show clinical effect, due, in part, to the fact that biomarkers may not predict clinical outcomes for potential disease modifying agents. These findings underscore the need for innovative approaches to clinical study design for measuring the effect of treatment.

Elenbecestat (E2609) is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, elenbecestat (E2609) inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in cerebrospinal fluid (CSF) and plasma (rat, guinea pig, and monkey). In humans, elenbecestat (E2609) has been shown to inhibit BACE1 enzyme activity in CSF and lower the levels of Aβ, including amyloid beta monomer from amino acid 1 to x (Aβ[1-x]), Aβ(1-40) and Aβ(1-42), in CSF both in vitro and in vivo. See the Investigator's Brochure for additional information. The target indication for elenbecestat (E2609) is therefore treatment and disease modification of AD.

The present clinical study is a Phase 2 study for the elenbecestat (E2609) program, and is designed to establish safety in subjects with Mild Cognitive Impairment due to Alzheimer's Disease/Prodromal Alzheimer's Disease (referred to as MCI/Prodromal throughout the protocol) and in subjects with mild to moderate AD. (revised per Amendment 05) This study will include a Core Study of approximately 32 months (including the Prerandomization and Randomization Phases) and an Open-label Extension (OLE) Phase of up to 27 months.

(revised per Amendment 07) Results from the Core Study will guide both the decision to move into Phase 3 development and the selection of the dose strengths to be taken into Phase 3.

In the MCI/Prodromal and mild to moderate AD population, the Core Study will compare placebo and 3 oral doses of elenbecestat (E2609) (5, 15, and 50 mg) administered once daily (QD) for 18 months. (revised per Amendment 05)

The Core Study will include interim evaluations of the pharmacokinetic (PK), pharmacodynamic (PD), safety, and tolerability of chronic dosing with elenbecestat (E2609). (revised per Amendment 05) Furthermore, there will be close monitoring of safety by an independent data safety monitoring board (DSMB), including a formal safety review as soon as the randomized subjects (n=60, ±20%) have completed at least 12 weeks of treatment, have discontinued study drug or have withdrawn from the study. (revised per Amendments 04 and 05) The study also includes a number of exclusion criteria, specific blinded safety monitoring procedures and safety criteria for discontinuation of study drug in light of the preclinical and clinical safety data collected to date following administration of elenbecestat (E2609).

The OLE Phase will evaluate the long-term safety and tolerability of elenbecestat (E2609); a detailed description of the OLE Phase is provided in Appendix 6. (revised per Amendment 07)

## 7.1 Results of Interim Evaluations

(revised per Amendment 06)

Unblinded interim evaluations of the safety and tolerability of elenbecestat (E2609) suggested favorable safety at all doses of elenbecestat (E2609). Additionally, analyses of the PD effects (reduction from baseline in CSF Aβ levels) of elenbecestat (E2609) 5, 15, and 50 mg per day have indicated that elenbecestat (E2609) 50 mg per day produced relatively high levels of CSF Aβ reduction (greater than 50%). Based on the results of these analyses, elenbecestat (E2609) 50 mg per day has been selected as the dose for Phase 3 development.

As elenbecestat (E2609) 5 and 15 mg per day will not be advanced clinically, subjects initially randomized to the elenbecestat (E2609) 5 and 15 mg per day treatment arms will be re-assigned in a blinded manner to the elenbecestat (E2609) 50 mg treatment arm provided that they will have at least 12 weeks of treatment remaining in the Randomization Phase. The purpose of this dose re-assignment is to further characterize the safety and tolerability of elenbecestat (E2609) 50 mg.

## 7.2 Nonclinical and Clinical Safety Data

The toxicity of elenbecestat (E2609) has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomologus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed

monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by elenbecestat (E2609) in a clinical setting. Further details of the nonclinical data to date with elenbecestat (E2609) can be found in the Investigator's Brochure.

The clinical program to date includes 6 Phase 1 studies:

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, single ascending dose (SAD) study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50-mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled MAD study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of elenbecestat (E2609) and the PD effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of elenbecestat (E2609). It also investigated the effects of elenbecestat (E2609) on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [$^{14}$C]-elenbecestat (E2609) in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of elenbecestat (E2609) under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) was a randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with elenbecestat (E2609). The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with elenbecestat (E2609). In elderly subjects treated with 50 mg of elenbecestat (E2609), tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum)

dose was associated with a small increase of QTc interval calculated using Fridericia's formula (QTcF) from baseline (14.9 msec at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of elenbecestat (E2609) might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that elenbecestat (E2609) altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of elenbecestat (E2609). A single dose of elenbecestat (E2609) up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, elenbecestat (E2609) administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of elenbecestat (E2609) on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP3A4] and carboxyesterase-2 [CES2]) increased by approximately 70% the area under the concentration × time curve (AUC) of elenbecestat (E2609). Consequently, strong inhibitors of CY3A4 will be prohibited in this study.

Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of elenbecestat (E2609). Therefore, no restrictions are required for the use of concomitant medications which are known to be inducers of CYP450 enzymes. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of elenbecestat (E2609) when coadministered with elenbecestat (E2609) but not when dosed at least 2 hours apart from elenbecestat (E2609). Elenbecestat (E2609) (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of elenbecestat (E2609). Therefore, on the basis of drug interaction considerations, the only restriction of concomitant medications is that for strong inhibitors of CYP3A4.

# 8 STUDY OBJECTIVES

Objectives for the OLE Phase are provided in Appendix 6. (revised per Amendment 07)

## 8.1 Primary Objective

(revised per Amendment 05)

The primary objective is:

- To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with elenbecestat (E2609) in MCI/Prodromal subjects and in subjects with mild to moderate AD (revised per Amendment 01)

## 8.2 Secondary Objectives

The secondary objectives are: (revised per Amendments 02 and 05)

- To characterize the plasma and CSF PK of elenbecestat
- To assess the effects of elenbecestat on Aβ(1-x) and Aβ(1-42) in CSF from 4 weeks and at 18 months of treatment

## 8.3 Exploratory Objectives

(revised per Amendments 01,02, 04, and 05)

The exploratory objectives are:

To explore the effects of elenbecestat (E2609) compared on CSF Aβ(1-40) and BACE1 measurements from 4 weeks and up to 18 months of treatment

To explore the effects of elenbecestat (E2609) compared with placebo on various biomarkers. Biomarkers to be explored may include, but not limited to:

a. CSF biomarkers of neurodegeneration (eg, total tau [t-tau], phosphorylated-tau [p-tau]) after 18 months of treatment
b. Plasma and CSF amyloid, and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment (revised per Amendment 06)
c. Total hippocampal atrophy at 12 and 18 months of treatment, as measured by volumetric magnetic resonance imaging (vMRI)
d. vMRI measurements including left and right hippocampal volume, whole brain volume, and total ventricular volume at 6, 12, and 18 months of treatment
e. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)

To explore the effects of elenbecestat (E2609) compared with placebo on clinical status at various time points during 18 months of treatment, and during posttreatment follow-up by assessment of:

a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-$cog_{14}$)
b. The Clinical Dementia Rating (CDR) scale
c. The Mini-Mental State Examination (MMSE)
d. The International Shopping List Task (ISLT)
e. The CogState Brief Battery (CBB)
f. The Functional Assessment Questionnaire (FAQ; (also known as the Functional Activities Questionnaire)

To explore the relationship between the treatment effects of elenbecestat (E2609) on measured clinical efficacy scales (eg, MMSE, CDR) and its effects on CSF amyloid, CSF amyloid isoforms, brain amyloid, and vMRI

To explore relationships between both elenbecestat (E2609) dose and exposure, with PD and safety endpoints

# 9 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan

This study is a multicenter, placebo-controlled, double-blind, parallel-group, randomized, dose-finding study with an OLE Phase of up to 27 months in subjects with MCI/Prodromal AD or mild to moderate AD. (revised per Amendments 01 and 07)

A common set of inclusion criteria, consistent with the NIA-AA clinical research criteria for MCI due to AD or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study consists of 3 phases: Prerandomization, Randomization, and OLE. The Prerandomization and Randomization Phases are referred to as the Core Study throughout the protocol. (revised per Amendment 07).

The Prerandomization Phase (up to 60 days, plus an additional window of up to 30 days if required [revised per Amendment 02]) will consist of a Screening Visit and a Baseline Visit. Screening assessments will be organized into 4 tiers; see Section 9.5.2.2, Table 6, and Figure 2.

All screening assessments must be completed, and eligibility to continue to the Baseline Period confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

All subjects (MCI/Prodromal and mild to moderate AD) will initially be randomized 1:1:1:1 to 4 treatment groups (5, 15, or 50 mg elenbecestat [E2609] or placebo) (revised per Amendments 01 and 05). Upon implementation of Amendment 06, at the next regularly scheduled visit, subjects receiving elenbecestat (E2609) 5 or 15 mg who have not yet completed Visit 17 (Week 66), will be re-assigned in a blinded manner to elenbecestat (E2609) 50 mg for the remainder of the treatment period. In order to maintain the blind, all subjects who have not yet had Visit 17 will go through the same procedures with the placebo-randomized subjects continuing to receive placebo and those randomized to elenbecestat (E2609) 50 mg continuing to receive 50 mg. (revised per Amendment 06)

All subjects who complete 18 months of treatment and 12 weeks of follow-up in the Core Study and who satisfy the entry criteria for the OLE Phase are eligible to enter the OLE Phase. During the OLE Phase, subjects will receive elenbecestat (E2609) 50 mg daily for up to 24 months (2 years).

An overview of the Core Study design is presented in Figure 1.

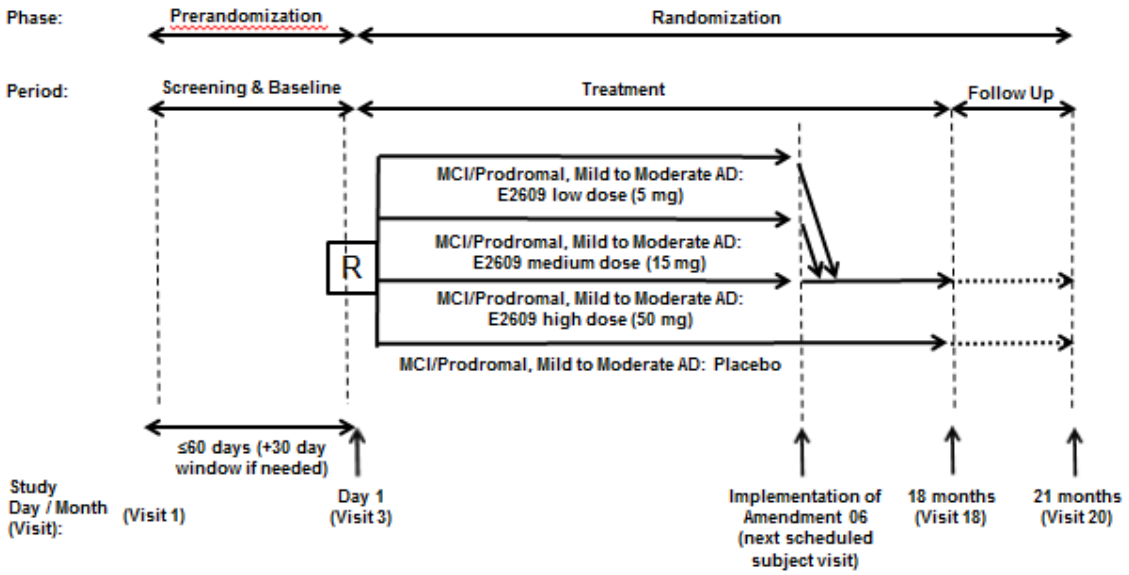



**Figure 1 Design of Core Study E2609-G000-202**

(revised per Amendments 01, 02, 05, and 06)

R = randomization, AD = Alzheimer's Disease, MCI = mild cognitive impairment.

This study will be limited to approximately 35 sites in the United States, with approximately 60 (±20%) eligible subjects randomized at Visit 3, 1:1:1:1 to 4 treatment groups within each clinical cohort. In addition to the placebo group, 3 doses of elenbecestat (E2609) will be used to reduce CSF Aβ levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/PD modeling shows these doses should achieve these targets when administered QD with food and will be evaluated based on the 4-week (or later) assessment of CSF Aβ(1-x) from subjects who provide voluntary consent for CSF measurement (see Section 9.4.4 ). (revised per Amendments 01, 02, 04, and 05) Safety data will be monitored in a blinded fashion on a regular basis.

In addition, approximately every 3 months from the time the 1st subject is randomized into the study through the time the last subject is randomized, an independent DSMB (including at least 1 immunologist) will review all safety data in an unblinded manner. (revised per amendment 06) The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. (revised per Amendments 01, 04, and 05)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

Interim analyses of the elenbecestat (E2609) plasma PK for all subjects and the elenbecestat (E2609) CSF PK and PD profiles will be performed on baseline data and samples collected after at least 4 weeks of treatment in the Core Study. (revised per Amendment 05 and 07) Refer Section 9.7.3 for more detail. These data will be used to evaluate the CSF PD effects of elenbecestat (E2609) doses, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels (see Section 9.4.4). The median and mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks or more of treatment for each dose of elenbecestat (E2609) and the 90% confidence interval (CI) for the median will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data and will relate the average steady state plasma concentration of elenbecestat (E2609) to steady state CSF Aβ(1-x) percentage reduction from baseline determined after at least 4 weeks of dosing. (revised per Amendments 01, 02, 03, and 04)

Once subjects have completed at least 12 weeks of treatment in the Core Study (or discontinued study drug early), an interim safety analysis will be conducted by Eisai and the DSMB. (revised per Amendments 01, 04, and 05) At the completion of this interim safety review, the frequency of subsequent unblinded safety reviews will be re-evaluated by the DSMB and the Sponsor and this information will be provided in the DSMB charter. (revised per Amendment 06) Subjects will continue study drug while the DSMB reviews all the available safety data. (revised per Amendment 05) At the time of this interim safety analysis, some subjects will have more than 12 weeks of safety data.

Interim analyses are planned and are discussed in Section 9.7.3. (revised per Amendment 03)

Based on the results of the interim analyses, the elenbecestat (E2609) 50 mg dose has been chosen as the clinical dose for the Phase 3 studies. In order to collect additional safety data for elenbecestat (E2609) 50 mg, subjects randomized to elenbecestat (E2609) 5 or 15 mg in this study will be re-assigned to elenbecestat (E2609) 50 mg if and only if these subjects have at least 12 weeks of treatment remaining in the Randomization Phase following study drug dose re-assignment. Therefore, subjects who completed Visit 17 assessments prior to the implementation of Amendment 06 will remain on their original randomized dose. As study drug dose re-assignment will occur in a blinded manner, a 4-week interim safety assessment following study drug re-assignment will be required for all subjects. (revised per Amendment 06)

### 9.1.1 Prerandomization Phase

The Prerandomization Phase includes a Screening Visit and a Baseline Visit. All Screening Visit assessments must be completed and eligibility to progress must be confirmed before any Baseline Visit assessments are performed. All Screening Visit and Baseline Visit assessments must be completed within 50 days (plus an additional window of up to 30 days if required [revised per Amendment 02]) and a window of no more than 10 days is to be observed between the completion of all Baseline Visit assessments (including confirmation of eligibility following all Baseline Visit assessments) and randomization into the study at Visit 3 (revised per Amendment 02). Thus, the Prerandomization Phase will last for up to

60 days, plus an additional window of 30 days if required (revised per Amendment 02). The series of assessments conducted during this phase will determine eligibility for randomization into the study.

Inclusion criteria are discussed in Section 9.1 and detailed in Section 9.3.1. Before randomization, the clinician will provide a judgment on the classification of a subject as either MCI/Prodromal or likely mild to moderate AD. (revised per Amendment 01) This judgment may be discussed and reviewed with the Sponsor or Sponsor's representative, as necessary.

Results of the Screening safety magnetic resonance imaging (MRI) will be valid for 90 days from the date of scanning. Results of the lumbar puncture (LP) from subjects who voluntarily consent for CSF measurement will be valid for 90 days from the date of testing. Results of Screening PET scans conducted specifically for this study and for use in the longitudinal analyses will also be valid for 90 days from the date of scanning. These assessments will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. Historical PET scans used for determination of eligibility only (ie, not used for the longitudinal analyses) are valid for 12 months. (revised per Amendment 02)

#### 9.1.1.1 Screening Period

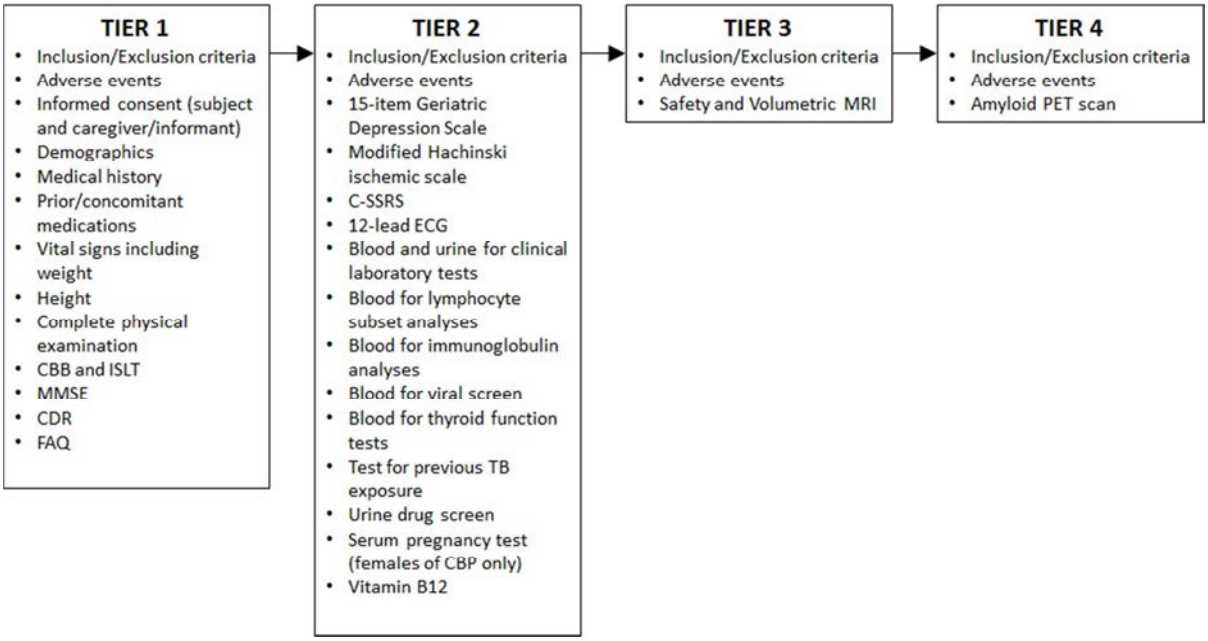
The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and caregiver or informant, and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained from both the subject and the caregiver or informant. The caregiver or informant needs to be present at this visit.

Study site personnel will interview the subject and caregiver or informant to obtain demographic and clinical information as described in Table 6, and will review inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2 and perform any required assessments in order to complete these criteria. Prior medications and medications currently being taken by the subject will be reviewed (see Section 9.4.7). The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

Clinical assessments for eligibility will be conducted during the Screening Visit as described in Table 6 and Figure 2.

Every effort should be made to conduct these assessments in the morning, but if this is not possible, they should be conducted at the same time of day at all subsequent visits. The screening assessments/procedures have been organized into 4 distinct tiers (Table 6 and Figure 2). All assessments/procedures in each tier should be completed, and eligibility to continue screening in the study confirmed, before any assessments/procedures from the next

tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures as long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. (revised per Amendment 01)




## Figure 2 Assessments to be Performed at Screening by Tier

CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), ISLT = International Shopping List Task (immediate and delayed recall), MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PET = positron emission tomography, TB = tuberculosis.

Cognitive assessments (Tier 1) are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). The recommended order of assessments at Screening is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. (revised per Amendment 02) The investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session (Tier 3).

Amyloid PET imaging will be used to confirm all subjects have amyloid deposition in the brain (Tier 4). An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. If an historical amyloid positive PET scan is being used, it should be submitted to the central PET reading group after the subject has completed and passed all Tier 1 assessments. (revised per Amendment 02)

#### 9.1.1.2 Baseline Period

All Screening Visit assessments must be completed (and eligibility to progress confirmed) before any Baseline Visit assessments are performed. The Baseline Visit assessments (per Table 6 and Section 9.5.1.2) are to be completed as soon as possible after completion of the final Screening Visit assessment (ie, PET scan) such that all Screening Visit and Baseline Visit assessments are completed within 50 days, plus an additional window of up to 30 days if required. (revised per Amendment 02)

Inclusion and exclusion criteria will again be reviewed, vital signs including weight will be recorded, and a 12-lead ECG will be conducted in triplicate. A routine physical examination will be conducted and a dermatological assessment and neurological examination (including the Brief Smell Identification Test [Sensonics Inc.]) will be performed. (revised per Amendment 04) A urine pregnancy test will be conducted for females of childbearing potential. Blood will be collected from all subjects for clinical chemistry and hematology, lymphocyte subset analyses, Ig analyses, and PD assessments. Blood samples will be collected and stored for determination of a subject's previous exposure to infective pathogens in the event of AEs that warrant further investigation occurring at a later point in the study. Psychometric assessments will be administered to the subject in the order stated in Table 6. The caregiver or informant needs to be present at this visit. The Columbia Suicide Severity Rating Scale (C-SSRS) will also be administered (Section 9.5.1.5.11).

For subjects who consent to CSF sample collection, a CSF sample will be obtained at this visit for PK and PD assessments (see Section 9.5.1.4). (revised per Amendment 02)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

Blood will be collected from all subjects for pharmacogenomic (PGx) analyses of apolipoprotein E (*ApoE*) and the N-acetyltransferase 2 (*NAT2)* phenotype of subjects enrolled in the study (see Section 9.7.1.7.2).

### 9.1.2 Randomization Phase

Subjects who complete the Baseline Visit assessments, and are eligible based on the inclusion and exclusion criteria (see Section 9.3.1 and Section 9.3.2), will begin the Randomization Phase no more than 10 days after completion of the Baseline Visit assessments and confirmation of the eligibility of the subject based on the results of all the Baseline Visit assessments (revised per Amendment 02).

The Randomization Phase will consist of a Treatment Period of 78 weeks duration and a Follow-up Period of 12 weeks after the last dose of study drug.

#### 9.1.2.1 Treatment Period

Subjects will be randomized at the beginning of the Treatment Period and will receive study drug or placebo, to be administered orally QD with food. Double-blinding to study drugs will be in effect throughout the Treatment Period. (revised per Amendment 06)

Safety criteria for discontinuation of study drug are detailed in Section 9.3.3.

Subjects will attend the study site every week for the first 4 weeks after beginning study drug, then fortnightly until 12 weeks have elapsed since first dose. Visits will then be conducted at 16, 20, 26, 39, 52, 65, and 78 weeks after the first dose.

#### 9.1.2.2 Early Discontinuation

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug. (revised per Amendments 04 and 05)

#### 9.1.2.3 Follow-up Period

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 4 posttreatment Follow-Up Visits: 2, 4, 8, and 12 weeks after the last dose of study drug. If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the posttreatment Follow-up Period. (revised per Amendment 04)

The end of the study will be defined as the date of the clinical database lock (ie, when all study data are collected and data validation is completed).

As required by some regulatory agencies, the following estimates are provided:

- The study will begin in Nov 2014 and is projected to end by Apr 2018. (revised per Amendment 05)
- The maximum estimated period for each subject on study is anticipated to be approximately 2 years.

### 9.1.3 Open-label Extension Phase

A complete description of the OLE Phase is provided in Appendix 6; key features are summarized below. (revised per Amendment 07)

After completing all Visit 20 follow-up procedures for the Core Study, eligible subjects will have the option to participate in the OLE Phase within 4 weeks of Core Study Visit 20. These subjects may transition to the OLE Phase immediately following Visit 20 (on the same day) if the decision to proceed with the OLE Phase has been made at that time. The Medical Monitor must be contacted if Visit 21 (start of the OLE Phase) is to occur more than 4 weeks after Visit 20.

For all subjects, assessments performed at Visit 20 may serve as the Visit 21 (start of the OLE Phase) results with the following exceptions: laboratory assessments and vital signs must be repeated if Visit 21 occurs more than 10 days after Visit 20.

Subjects who are eligible and who consent to participate in the OLE Phase will be administered elenbecestat (E2609) 50 mg daily at Visit 21. Subjects with pending INR and serum pregnancy test results (females subjects of child bearing potential only) but who are otherwise qualified may begin OLE dosing at Visit 21; however, these subjects must discontinue study drug immediately if either test result meets the exclusion criteria.

During the OLE Phase, safety assessments will continue to be monitored and all AEs and SAEs will be recorded. Vital signs, hematology, blood chemistry, and urine values will be monitored at every scheduled visit. Clinical assessments (MMSE and FAQ) will be administered every 3 months. Blood for PD analyses will collected after 12 and 24 of OLE treatment. All subjects will be assessed using safety MRIs and vMRI measurements at the end of the OLE Phase.

#### 9.1.3.1 Early Discontinuation

Subjects who prematurely discontinue study drug for any reason will undergo an ED Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug.

#### 9.1.3.2 Follow-Up

All subjects, regardless of whether they complete all 24 months of treatment in the OLE Phase or prematurely discontinue study drug will complete 2 posttreatment Follow-Up Visits at 4 and 12 weeks after the last dose of study drug. If clinically indicated, more frequent safety assessments can be conducted as part of Unscheduled Visits during the OLE Follow-up Period.

## 9.2 Discussion of Study Design, Including Choice of Control Groups

### 9.2.1 Overview

The primary objective of the study is to assess the safety and tolerability of daily dosing with elenbecestat (E2609) in subjects with MCI/Prodromal AD and in subjects with mild to moderate AD. Immunological and hematological parameters will also be assessed. (revised per Amendment 04)

The inclusion criteria for the MCI/Prodromal cohort will be consistent with the NIA-AA criteria for MCI due to AD (Albert, et al., 2011) and with the definition of Prodromal AD per Dubois et al., 2010 (see Section 9.2.2).

There is no active or positive control for this study as at this time, there is no cure for AD, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

Secondary endpoints include CSF PK and plasma PK parameters of elenbecestat (E2609) based on population PK analysis and the percentage reduction of Aβ(1-x) and Aβ(1-42) in CSF relative to baseline from 4 weeks and up to 18 months of treatment. The intrinsic and extrinsic factors on the PK characteristics will also be explored.

Exploratory endpoints include CSF Aβ(1-40) and BACE1 measures as well as CSF biomarkers of neuronal degeneration (eg, t-tau and p-tau), volumetric MRI measurements, plasma amyloid measurements, brain amyloid levels as measured by amyloid PET and clinical assessments. (revised per Amendment 05) Exploratory endpoints including assessments of efficacy, safety, and other biomarkers are also included.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups (Section 9.7.4) Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

The rationale for the selection of doses used in the study is provided in Section 9.4.4.

### 9.2.2 Rationale for Study Population

By the time AD progresses to dementia, with loss of functional capabilities, the amyloid load in the brain is approaching a plateau and significant neurodegeneration has occurred (Jack, et al., 2010). Consequently, there is a growing view within the AD field that it may be necessary to initiate disease modifying treatments earlier, before the onset of clinical dementia (Aisen, et al., 2010). However, this hypothesis remains to be demonstrated with clinically effective therapies, and may not apply to all therapeutic classes, it is possible that this consideration explains the failure of the humanized monoclonal antibody bapineuzumab (which targeted brain amyloid) to demonstrate clinical efficacy in late-phase studies in mild to moderate AD dementia. (revised per Amendment 01)

With this consideration taken into account, the primary clinical population of focus in this study is subjects with MCI/Prodromal AD. The mechanism of action of a BACE1 inhibitor where amyloid production is reduced means elenbecestat (E2609) is more likely to be efficacious (ie, slow disease progression) the earlier in disease progression treatment is started, where limited neurodegeneration has occurred and associated clinical deficits are at a minimum. However, since the effect of BACE1 inhibition along the AD continuum remains to be characterized, elenbecestat (E2609) will also be evaluated for its profile in mild to moderate stages of AD, in the event data emerge supporting its use beyond MCI/Prodromal AD. Indeed, recent data support the notion of continued progression of amyloid pathology even in these later stages of the disease (Hu, et al., 2015), although at a slower pace, suggesting a positive effect of BACE inhibition and amyloid beta reduction cannot be ruled out even in the later stages of the disease trajectory. Hence, in this study, elenbecestat (E2609) will be assessed in subjects with disease states ranging from MCI/Prodromal to mild and even moderate AD. (revised per Amendment 01)

As discussed, efficacy is more likely to be observed in subjects with MCI/Prodromal AD but there is the possibility that efficacy will also be evident following administration of an amyloid modifying agents such as elenbecestat (E2609) in subjects with more advanced disease such as mild to moderate AD. (revised per Amendment 01) For example, a study of tarenflurbil, a selective Aβ(1-42)-lowering agent, on cognition and function in subjects with mild to moderate AD showed the subjects with mild AD had lower rates of decline than those in the placebo group in activities of daily living and global function; however, slowing of cognitive decline did not differ significantly (Wilcock, et al., 2008). Similarly, differential effects on cognitive measures have been observed with solanezumab, where some benefit from treatment was observed in subjects with mild AD, although studies with solanezumab were considered to have failed to improve cognition or functional ability significantly (Doody, et al., 2014). Therefore, it is relevant to compare the effect of the BACE1 inhibitor elenbecestat (E2609) in 2 different subject populations that differ in terms of AD severity before the initiation of large Phase 3 clinical studies. (revised per Amendment 01)

### 9.2.3 Rationale for Clinical Endpoints

The 14-item version of the ADAS-Cog will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007).

The CDR is a clinical global rating scale requiring the interviewing of both the subject and an informant who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975)

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al,. 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials on the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson et al., 2011, Lim, et al., 2012a, Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with elenbecestat (E2609) treatment.

The CBB is a brief, computer-administered cognitive test battery that requires approximately 10 minutes for administration (Darby, et al., 2012; Fredrickson, et al., 2008; Maruff, et al., 2009). The CBB has been used to detect cognitive impairment in several neurodegenerative conditions including the measurement of cognitive function in healthy older adults and in

adults with clinically diagnosed AD and prodromal AD (Darby, et al., 2009; Hammers, et al., 2012; Lim, et al., 2012a; Lim, et al., 2012b). The administration, scoring, and reporting of the CBB is automated and highly standardized, resulting in cognitive paradigms that have been well-validated in neuropsychological and cognitive studies (Fredrickson, et al., 2008; Maruff, et al., 2009). See Section 9.5.1.3.1 for further details.

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression. Volumetric magnetic resonance imaging is discussed in Section 9.2.4.4.

## 9.2.4 Rationale for Biomarkers

### 9.2.4.1 Overall Rationale

The biomarker strategy for this study includes the following aims:

- To establish an amyloid load in the brain at study entry (via the PET eligibility inclusion criterion)
- To evaluate safety (principally by MRI)
- To evaluate a PD effect in terms of both Aβ in CSF and brain amyloid assessed by amyloid PET and to establish that this PD effect is maintained long-term (revised per Amendment 02)
- To evaluate disease modification through longitudinal assessments of vMRI, amyloid PET, and CSF biomarkers of neurodegeneration (t-tau and p-tau)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

### 9.2.4.2 Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect of elenbecestat (E2609) on Aβ(1-40) +Aβ(1-42) and other C-terminally truncated Aβ peptides such as Aβ(1-38) through inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using [$^{11}$C]PiB, suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases in CSF Aβ concentrations that are seen in AD are believed to be related to this decrease in brain Aβ availability.

Both t-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni and Bhaskar, 2012). CSF tau measurements have been

correlated with cerebral atrophy, while their ratios with Aβ42 have provided useful predictors of cognitive decline and progression to dementia due to AD. Rebalancing dysregulated amyloid production early in the process may positively affect the neurodegenerative process and thus affect these markers and benefit the disease trajectory. Therefore, monitoring these markers in conjunction with amyloid imaging may provide further supportive evidence of disease modifying effects. (revised per Amendment 04)

Baseline levels of Aβ(1-42), t-tau, and p-tau will also help elucidate the extent of AD pathology at entry to the study and can be combined with baseline levels of *ApoE4* genotyping in addition to the baseline imaging variables to help explain differences in treatment response.

The study will be stratified at randomization for *ApoE4* gene status in order to account for any *ApoE* status by treatment interaction or *ApoE* status by amyloid-related imaging abnormalities risk interaction.

#### 9.2.4.3 Amyloid PET

Amyloid PET imaging will be used in this study for 2 primary reasons: 1) to confirm the presence of AD pathology in the brain of subjects with MCI/Prodromal AD or mild to moderate AD at entry to the study; and 2) to evaluate the effects of elenbecestat (E2609) on amyloid levels in the brain, both by whole brain analysis (the average of 5 to 6 cortical regions) and brain region analysis. (revised per Amendment 01)

Longitudinal amyloid PET imaging will be conducted after 18 months of treatment in the Core Study (or at ED, providing the subject has received at least 39 weeks of study drug) as an exploratory measure of the potential disease-modifying effects of elenbecestat (E2609). (revised per Amendment 07) Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses). (Revised per Amendments 02 and 05)

#### 9.2.4.4 vMRI

Volumetric imaging will be used to evaluate the effects of elenbecestat (E2609) on rates of atrophy across the different dose groups during the Core Study and to provide support that effective treatment is associated with modification of disease course (exploratory endpoints in the Core Study and OLE Phase). (revised per Amendments 01 and 07) A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. Clinically efficacious doses are predicted to be associated with a slowing in the rate of hippocampal atrophy compared with rates observed in the placebo and non-efficacious dose groups. Treatment effects on left and right hippocampal, whole brain, and total ventricular volumes are exploratory endpoints.

Annualized rates of change of 2% to 3% have been reported for the AD brain compared with 1% in MCI and <1% in age-matched controls (Hua, et al., 2010, Leung, et al., 2010).

However, subjects with MCI due to AD-dementia (CSF Aβ <192 pg/mL or positive amyloid imaging) show rates of atrophy comparable to those observed in subjects with AD-dementia (Hua, et al., 2009; Hua, et al., 2010; Leung, et al., 2010; Morra, et al., 2009), supporting the notion that such subjects are on similar trajectories as those with mild AD-dementia. Lower levels of CSF Aβ42, amyloid positivity on PET imaging, and higher levels of CSF t-tau in addition to the presence of the *ApoE4* allele have all been associated with greater rates of brain atrophy (Fjell, et al., 2010a; Fjell, et al., 2010b) and will be entered as covariates in various analyses. Hippocampal atrophy has also been shown to predict clinical progression independently of amyloid levels in the brain (Jack, et al., 2010), and this measure will be entered as a covariate in the analysis of the clinical endpoints along with the aforementioned variables.

Brain volume (total ventricular volume, whole brain, temporal lobe) generally shows a modest correlation with performance on a number of cognitive scales (Hua, et al., 2009; Hua, et al., 2010; Freeborough, et al., 1997; Leung, et al., 2010). Using volumetric analysis performed at 6-month intervals during the Core Study and at the end of the OLE Phase, these relationships and the effects of elenbecestat (E2609) treatment will be explored further. (revised per Amendment 07) Recent advances in analysis software have made structural imaging more sensitive to detect small changes and able to reliably measure rates of atrophy at these intervals, particularly in the posterior parietal and the lateral temporal regions during the early stages of disease (Hua, et al., 2009; Hua, et al., 2010). Given these observations, a demonstration of significant slowing or stabilization in the rate of atrophy in response to treatment, compared with placebo, will offer further support for disease modification.

### 9.2.5 Clinical Risks and Mitigation Strategy

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with elenbecestat (E2609), and to mitigate clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of Core Study treatment and 24 months of OLE Phase treatment in this Phase 2 study. (revised per Amendment 07) These safety aspects include the following:

- Immunology-related and infection-related exclusion criteria for both the Core Study and the OLE Phase (revised per Amendment 07)
- Review of unblinded safety data by an independent DSMB at regular intervals
- Safety criteria for study drug discontinuation based on CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cell) during the Core Study and absolute lymphocytes during the OLE Phase (revised per Amendment 07)
- Safety criteria for study drug discontinuation during the Core Study and OLE Phase based on skin rash, reoccurrence of herpes virus infections including any oral herpes, genital herpes or shingles, other infections, MRI changes, ECGs, and pregnancy. (revised per Amendment 07)

In addition to the features above, other safety aspects of this study designed to mitigate clinical risk include the following:

- Blinded safety data will be monitored by Eisai at regular intervals during the course of the study
- Routine safety assessments will include the monitoring and recording of all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and dermatological assessments at regular intervals. (revised per Amendment 07) AEs that might indicate signals of possible drug abuse potential will require a detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events. To assess potential immunomodulatory effects, peripheral blood mononuclear cells (PBMCs) will be collected at baseline, during treatment, and posttreatment.

As per the communication from the Food and Drug Administration (FDA) in Aug 2013, there are concerns that hypopigmentation of the skin and mucous membranes may occur with BACE1 inhibitory drugs. Although no such effects have been seen with elenbecestat (E2609) to date, assessments using standardized photography will be performed by a central reviewing dermatologist at regular intervals during the Core Study. During the OLE Phase, a dermatologic assessment will be performed by the investigator at every scheduled visit. Every assessment will specifically include evaluation of any areas of depigmentation or any rash. (revised per Amendment 07) Dermatological assessments will be supplemented with a specific question to subjects regarding skin changes at each visit. Any such changes could be referred to the central reviewing dermatologist, and to a local dermatologist if needed, for further evaluation. See Section 9.5.1.5.8 and Appendix 6 for further details. (revised per Amendment 07)

- Baseline and on-study blood will be taken and stored for all subjects during the Core Study and OLE Phase. (revised per Amendment 02 and 07) DNA samples and CSF samples (for all subjects who consent to CSF sample collection) will be taken and stored during the Core Study. (revised per Amendment 02 and 07) These samples may be tested in the event that a subject develops AEs that warrant further investigation (eg, if a subject develops a treatment-emergent infection) (see Section 9.5.1.2.2 and Appendix 6). (revised per Amendment 07)
- Central reading of safety brain MRI assessments (including any MRI evidence of demyelination) will be performed at Screening, at approximately 6-month intervals during the Core Study Treatment Period, and at the final Follow-Up Visit during the Core Study. (revised per Amendment 07) MRI assessments will also be performed at the end of the OLE Treatment Period. In addition, safety brain MRI assessments may be performed as an unscheduled assessment if clinically indicated. (revised per Amendment 07)
- Full neurologic examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. Details of the neurologic examination are given in Section 9.5.1.5.9 and Appendix 6. (revised per Amendment 07)

- Cognitive decline will be assessed as a safety assessment during the Core Study (ADAS-cog$_{14}$, MMSE, and CBB) and during the OLE Phase (MMSE). (revised per Amendment 07) Of particular importance will be the assessment of reaction time testing using the detection and identification tasks on the CBB during the Core Study. (revised per Amendment 07)
- During the Core Study, an assessment of suicidality using the C-SSRS will be performed at Screening, Baseline, and at regular intervals during the Treatment and Follow-up Period (see Section 9.5.1.5.11). During the OLE Phase, C-SSRS will be performed at Visit 21 (start of OLE treatment) and Visit 32 or the ED Visit (end of OLE treatment). Additional clinical assessments of reported suicidal thinking and behavior will be performed by the investigator at every scheduled visit during the OLE Phase (see Appendix 6). (revised per Amendment 07)
- All subjects, regardless of whether they complete all 18 months of treatment or prematurely discontinue study drug during the Core Study, will have at least 4 off-treatment Follow-Up Visits during the Core Study (2, 4, 8, and 12 weeks after the last dose of study drug). Subjects who complete or prematurely discontinue study drug during the OLE Phase will have 2 off-treatment Follow-Up Visits at 4 and 12 weeks after the last dose of study drug. (revised per Amendment 07)
- More frequent safety assessments can be made as unscheduled assessments/visits during the off-treatment Follow-Up period, if clinically indicated. (revised per Amendment 04)
- An ophthalmic examination will be conducted at Baseline and if the subject experiences visual disturbances during the course of the Core Study (see Section 9.5.1.2.1).

## 9.3 Selection of Study Population

Approximately 60 (±20%) eligible MCI/Prodromal or mild to moderate AD subjects will be randomized at approximately 35 sites in the United States (revised per Amendments 02 and 04). There will be no restriction to the number of subjects from either population.

Subjects who do not meet all of the inclusion criteria in Section 9.3.1 or who meet any of the exclusion criteria in Section 9.3.2 will not be eligible to receive study drug during the Core Study. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria provided in Appendix 6 will not be eligible to enter the OLE Phase. (revised per Amendment 07)

### 9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD (Albert, et al., 2011) or AD dementia (McKhann, et al., 2011) and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at Screening Visit 1:**

(revised per Amendment 02)

a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation

b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT. Alternatively, cognitive impairment of at least 0.5 SD from age-adjusted norms in delayed recall on the ISLT plus impairment of at least 1 SD from age-adjusted norms in at least 1 other computerized learning and memory test (ISLT immediate recall, or 1 of the learning and memory components of the CBB). (revised per Amendment 02)

c. FAQ ≤24 (revised per Amendment 01)

d. MMSE ≥16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading; an historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group (revised per Amendment 02)

3. Male or female, age 50 to 85 years, inclusive at time of consent

4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.

5. If receiving acetylcholinesterase inhibitors (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the Baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.

6. Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization

### 9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or MRI
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and <1cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could, in the opinion of the investigator, confound the MCI/Prodromal or mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendments 01 and 02)
7. A score of ≥8 on the 15-item Geriatric Depression Scale (GDS) at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the LLN for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
12. Any contraindications to LP for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not

limited to obesity). Only applicable to subjects consenting to CSF sample collection (revised per Amendment 02)

13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of Ig deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization.
20. Any active infection within the last 4 weeks prior to randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below population-adjusted LLN at Screening or Baseline and confirmed by a repeat test conducted 1 week after the initial test. The population-adjusted LLN for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are 396, 157, and 74 cells/µL respectively. See Appendix 5. (revised per Amendment 02)
23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the Investigator and the Medical Monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of clinical immunodeficiency. The discussion with the Medical Monitor should include a detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)
24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline

25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate ECGs. A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute (bpm) at Screening or Baseline
29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.
33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo). Diagnosis of an underlying disease causing hypopigmentation is not necessary for exclusion if the clinical presentation is consistent with such a condition. Hypopigmentation associated with scarring need not be exclusionary. (revised per Amendment 02)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the C-SSRS suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place

during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.

39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period or for 28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.
    - Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
    - (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]). (revised per Amendment 04)

### 9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may discontinue study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to stop study drug or withdraw from the study at any time for any reason.

Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). Follow-Up Visits will also be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug in the Core Study (see Section 9.1.2.3), and 4 and 12 weeks after the last dose of study drug in the OLE Phase (see Appendix 6). (revised per Amendments 04, 05 and 07)

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the Subject Disposition eCRF page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study drug and withdraws from the study at the same time, the ED Visit will be followed (see Section 9.5.5).

Safety-related criteria for discontinuation of study drug during the Core Study include the following: (revised per Amendments 07)

a. A study drug discontinuation threshold will be set based on absolute counts of CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells). The discontinuation threshold will be set at below the level of the population-adjusted LLN (CD4=396 cells/µL; CD8=157 cells/µL; and CD19=74 cells/µL), at a level that represents a greater risk of opportunistic infection in the treated population. (revised per Amendment 02) For CD4 (T helper cells) the discontinuation threshold is 250 cells/µL. For CD8 (cytotoxic T cells) and CD19 (B cells) the discontinuation thresholds are 150 cells/µL and 50 cells/µL, respectively. Any subject who has CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below the discontinuation threshold as confirmed by a repeat test conducted within 1 week of the initial test but who has no clinical signs or symptoms of infection, will have study drug temporarily suspended for at least 2 weeks but no more than 4 weeks. During this period of study drug suspension, lymphocyte subset counts and complete blood count (CBC) with differentials will continue to be tested weekly until CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) have all returned to greater than the population-adjusted LLN after which time study drug can be resumed. Testing of lymphocyte subset counts and CBC with differentials is required weekly for 4 weeks following resumption of study drug administration. Temporary suspension and rechallenge with study drug is only permitted once for any given subject. If the lymphocytes and CD counts do not return to greater than the population-adjusted LLN within 4 weeks from the start of temporary suspension the subject will need to be permanently discontinued from study drug. (revised per Amendment 04)

b. Subjects with CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between the population-adjusted LLN and the discontinuation threshold will have lymphocyte subset counts performed on a weekly basis. (revised per Amendments 02 and 04) During the early stages of the treatment period, where visits are conducted weekly (ie, Visits 4, 5, 6, and 7), lymphocyte subsets are already scheduled to be measured on a weekly basis and so additional visits or blood draws are not required. (revised per Amendment 02) For these subjects, the decision as to whether the subject remains on study drug or is to be discontinued from study drug will be based upon clinical judgment and will take into account any clinical presentation in addition to the

lymphocyte subset counts. These subjects may continue with treatment if there is no clinical evidence of infection. They will be discontinued from study drug if they have infections of a moderate to severe intensity (eg, subjects whose infections are not localized, or are systemically unwell, or who require systemic anti-infective drug treatment).

**Table 1 Study Drug Actions for Lymphocyte Subset Absolute Counts**

| Lymphocyte subset absolute counts | Action | Decision to continue, discontinue, or temporarily suspend study drug |
|---|---|---|
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold and no clinical signs or symptoms of infection | Retest within 1 week along with<br>CBC with differentials | If retest performed within 1 week confirms lymphocyte subset counts below the discontinuation threshold, temporarily suspend study drug for between 2 and 4 weeks. Continue weekly testing of lymphocyte subsets and CBC with differentials. Rechallenge with study drug allowed when CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts all greater than population-adjusted LLN. Temporary suspension and rechallenge permitted only once for each subject. |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between population-adjusted LLN and discontinuation threshold | Lymphocyte subset counts (and CBC with differentials) to be performed weekly until lymphocyte subset counts return to ≥ population-adjusted LLN | Decision will be based upon lymphocyte subset counts and clinical judgment |

LLN = lower limit of normal, CBC = complete blood count.

(Table revised per Amendments 02 and 04)

c. Subjects with clinical evidence of infection will have their CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts measured. Blood and other biological samples will also be collected for investigations of infective pathogens (eg, serological tests, quantitative polymerase chain reaction, microscopy, and culture) where appropriate. In subjects with infection, if any of their absolute cell counts meets the discontinuation thresholds, study drug will be discontinued. All subjects with severe infections will be discontinued from study drug. All subjects with herpes zoster (shingles) or ocular herpes infections will be discontinued from study drug, regardless of severity of presentation. Subjects with mild or moderate infection may continue treatment with study drug unless otherwise clinically indicated or otherwise specified below. Specifically, when any of the CD4 (T helper cells), CD8 (cytotoxic T cells), and

CD19 (B cells) absolute counts are between the population-adjusted LLN and the discontinuation thresholds, subjects with infections of moderate intensity will be discontinued from study drug (eg, subjects whose infections are not localized, or subjects who are systemically unwell, or who require systemic anti-infective drug treatment). All subjects with infection who are discontinued from study drug will be followed for a period of 12 weeks or until the infection resolves/ stabilizes or until the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts have returned to greater than population-adjusted LLN (whichever comes latest). (revised per Amendments 02 and 04)

**Table 2 Study Drug Actions for Lymphocyte Subset Absolute Counts and Infection**

| Criterion | Severity of Infection | | | |
|---|---|---|---|---|
| | None | Mild | Moderate | Severe |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold | If confirmed with repeat testing within 1 week, then temporarily suspend study drug as per instructions above. | Discontinue study drug | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between population-adjusted LLN and discontinuation threshold | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts always > population-adjusted LLN | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated (See (e) for exception) | Discontinue study drug |

LLN = lower limit of normal.

(Table revised per Amendments 02 and 04)

d. A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (see (e) for exception), will be discontinued from study drug and a dermatological consult will be requested regardless of whether the rash is considered drug-related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatological consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

e. Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

f. Development of any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. If discontinued from study drug, subjects will undergo an ED Visit within 7 days after discontinuation and will attend the Follow-Up Visits 2, 4, 8, and 12 weeks after the last dose of study drug. They will also undertake an Unscheduled Visit (with MRI) at approximately 4 weeks after the visit at which such MRI features were first identified. An MRI will also be performed at approximately the time of the final Follow-Up Visit (Visit 20). Additional visits for safety may be arranged if clinically indicated in the opinion of the investigator, including after 12 weeks after the last dose of study drug. At any time during the treatment period, subjects who have asymptomatic, treatment-emergent microhemorrhages as detected by MRI, but none of the features which merit discontinuation of treatment (ie, vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic treatment-emergent microhemorrhage) may continue with treatment. These subjects will have safety assessments (including MRI) at approximately 4 weeks after the visit at which such MRI features were found. They will also continue with the scheduled MRI scans. Additional unscheduled MRI scans may be arranged on an individual subject basis in discussion with the study medical monitor. (revised per Amendment 04)

g. A postdose ECG with an average QTcF interval >500 msec from triplicate ECGs

h. A postdose ECG with a QTcF interval increase from baseline >60 msec and a QTcF interval >450 msec as demonstrated from triplicate ECGs

i. Any seizure (motor or non-motor)

j. Pregnancy

Safety-related criteria for discontinuation of study drug during the OLE Phase are provided in Appendix 6. (revised per Amendment 07)

## 9.4 Treatments

### 9.4.1 Treatments Administered

For the Core Study, the test drug is elenbecestat (E2609) and the control drug is placebo. (revised per Amendments 07) All study drugs are to be administered orally, QD, with food.

Treatments to be administered during the Core Study are 5, 15, and 50 mg elenbecestat (E2609) or placebo prior to the implementation of Amendment 06, and 50 mg elenbecestat (E2609) or placebo after the implementation of Amendment 06 as shown in Figure 1. (revised per Amendments 01, 05, 06, and 07) Study treatment will begin on Day 1 (at the study site) following Randomization and will continue for approximately 78 weeks. Please refer to Table 7 and Section 9.5.1.4.1 for specific information on drug administration on days when PK sampling is to be performed.

Treatments to be administered during the OLE Phase are described in Appendix 6. (revised per Amendment 07)

Study drug doses will remain the same for each individual subject unless the interim PK/PD analysis determines that an entire dose level requires adjustment (Section 9.4.4). See Section 9.3.3 for safety-related discontinuation criteria of study drug. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

### 9.4.2 Identity of Investigational Product

Elenbecestat (E2609) tablets of 5-, 10-, and 25-mg dose strengths will be supplied. Placebo tablets of identical appearance will also be available. Each subject will receive 2 tablets, which combined will make up the required doses of elenbecestat (E2609) 5, 15, 50 mg, or placebo. The tablets will be supplied by the Sponsor in labeled blister packs. The product release certificates for elenbecestat (E2609) and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either elenbecestat (E2609) or placebo, or both (see Section 9.4.2.3 for labeling details).

#### 9.4.2.1 Chemical Name and Formula of Elenbecestat (E2609)

- Test drug code: E2609
- Generic name: Elenbecestat (pINN)
- Chemical name: International Union of Pure and Applied Chemistry
- *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

#### 9.4.2.2 Comparator Drug

Not applicable.

#### 9.4.2.3 Labeling for Study Drug

Elenbecestat (E2609) will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier (ID)
- Lot number/batch number
- Storage conditions, expiration date if necessary

#### 9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

### 9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups are described in Section 9.4.1. (revised per Amendments 01 and 05)

Randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized blister card identification numbers. At enrollment, the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 3), the IxRS will assign each subject a unique randomization number.

### 9.4.4 Selection of Doses in the Study

It is not known how the level of CSF or brain Aβ reduction is related to clinical efficacy. Therefore, in this study, initial doses will be selected such that at steady state, they will result in 25%, 50%, and 75% reduction in CSF Aβ levels from baseline to cover a broad range of PD effects. (revised per Amendment 06)

In Study 007, the relative bioavailability of a tablet formulation of elenbecestat (E2609) in the fed and the fasted states compared with the capsule formulation in the fasted state (used in Studies 001 and 002) was investigated. It was found that when the tablet form of elenbecestat (E2609) (50 mg) was administered with food, the exposure (ie, AUC) of the parent drug elenbecestat was higher, with lower maximum observed concentrations and reduced exposure to the metabolites, compared with either formulation in the fasted state.

Based on the PK/PD modeling using data from healthy volunteer Studies 001, 002, and 007, doses of 5, 15, and 50 mg QD administered as the tablet formulation with food in this study should achieve CSF Aβ reduction from baseline of approximately 25%, 50%, and 75% at steady state, respectively (Table 3).

**Table 3 Predicted Steady State Plasma PK Parameters and CSF Amyloid β Reduction From Baseline**

| Elenbecestat (E2609) Tablet Daily Dose (mg) With Food | Plasma Elenbecestat (E2609) | | | % Reduction CSF BACE1 Activity | % Reduction CSF Aβ(1-x) |
|---|---|---|---|---|---|
| | $C_{max,ss}$ (ng/mL) | $C_{ss,av}$ (ng/mL) | $AUC_{(0-24h)ss}$ (ng·h/mL) | | |
| 5 | 6.2 | 3.3 | 80.3 | 16.2 | 33 |
| 15 | 18.6 | 10 | 240.9 | 36.6 | 56 |
| 50 | 62.1 | 33.5 | 803.0 | 65.7 | 79 |

Aβ(1-x) = amyloid beta monomer from amino acid 1 to x, $AUC_{(0-24h)ss}$ = area under the concentration x time curve at steady state from time zero to 24 hours, BACE1 = beta-amyloid converting enzyme, CSF = cerebrospinal fluid, $C_{ss,av}$ = average steady-state concentration, $C_{max,ss}$ = maximum plasma concentration at steady state, PK = pharmacokinetics.

The PK/PD modeling described above, which was conducted using data obtained from healthy volunteers, has also been supported by modeling of data from subjects with an underlying AD pathology (Study 101). Furthermore, external data with another BACE1 inhibitor (MK-8931) showed a similar PD effect in AD patients as in healthy volunteers (Forman, et al., 2013). Therefore we are confident that the modeling of elenbecestat (E2609) effects in healthy subjects will be applicable for both MCI/Prodromal and mild to moderate AD dementia patients. (revised per Amendment 01)

The exposure of the highest dose in this study (50 mg QD tablet administered with food) is less than that of the 100 mg QD dose (capsule administered fasted) in Study 002.

The 100 mg QD dose administered for 14 days in Study 002 was well tolerated with no clinically significant changes in laboratory parameters, vital signs, or ECG parameters. On Day 15, for the 100 mg QD cohort in Study 002, there was a reduction of CD4 lymphocyte counts compared with placebo (CD4 lymphocyte counts on elenbecestat (E2609) decreased by 3.1% from baseline, whereas the placebo control showed an increase of 8.7%), but this decrease was less than that observed at doses of 200 mg (22.9% decrease) or 400 mg (17.3% decrease). No subject had infections or drug rash while receiving elenbecestat (E2609) 100 mg QD or at lower doses in Study 002, whereas at 200 and 400 mg QD, 4 subjects had symptomatic orolabial HSV1 relapses and 2 subjects at the highest dose had drug rash. The highest dose for Study 202 of 50 mg QD (tablet administered with food) is therefore expected to have a similar or better safety profile compared with the 100 mg QD capsule (administered fasted) in Study 002. Specific exclusion criteria, blinded and unblinded safety monitoring procedures, and safety criteria for discontinuation from study drug are included in this study in order to mitigate any immunology-related risk with elenbecestat (E2609), particularly in light of the progression from 14 days of dosing (Study 002) to 18 months of dosing in this study.

Interim analyses of the elenbecestat (E2609) plasma PK for all subjects and the elenbecestat (E2609) CSF PK and PD profiles will be performed on baseline data and samples collected after at least 4 weeks of treatment. These interim analyses, as well as analyses of safety data, will be performed on an ongoing basis. Refer Section 9.7.3 for more detail. The median and mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment for each dose of elenbecestat (E2609) and its 90% confidence interval for the median will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data and will relate the average steady state plasma concentration of elenbecestat (E2609) to steady state CSF Aβ(1-x) percentage reduction from baseline after at least 4 weeks of dosing. (revised per Amendments 01, 02, 03, 04, and 05)

Unblinded interim analyses have indicated elenbecestat (E2609) 50 mg per day produced relatively high levels of CSF Aβ reduction (greater than 50%) with an acceptable safety profile. As a result, elenbecestat (E2609) 50 mg has been selected as the dose for Phase 3 development. To gain a more comprehensive safety and tolerability profile of elenbecestat (E2609) 50 mg, subjects randomized to elenbecestat (E2609) 5 and 15 mg will be re-assigned to elenbecestat (E2609) 50 mg for the remaining of the 18-month treatment period with the provision that they will have at least 12 weeks of treatment remaining in the Randomization Phase. (revised per Amendment 06)

### 9.4.5 Selection and Timing of Dose for Each Subject

Elenbecestat (E2609) is administered orally, QD, with food. Study treatment will begin on Day 1 following randomization and will continue for approximately 78 weeks.

### 9.4.6 Blinding

Elenbecestat (E2609) and placebo will be administered as tablets of identical appearance during the Core Study.

During the Randomization Phase and Follow-Up Phase in the Core Study, subjects, caregivers/informants, and all clinical site personnel involved with the conduct and interpretation of the study, including investigators will be blinded to the treatment codes (double-blind). In order to make decisions about the remainder of the study as well as the full elenbecestat (E2609) clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. (revised per Amendment 03)

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (ie, those who are trained and certified to perform the various cognitive assessments that are undertaken in this study). Furthermore, at the site, the notes and reports relating to safety assessments must be kept separate from the notes and reports relating to efficacy, particularly for the CDR. (revised per Amendment 01)

Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

The PK/PD interim analyses will take place throughout the study as per Amendment 03 and will be conducted by an independent PK/PD scientist at the sponsor. Any additional changes to dose required for this study will be reflected in a further amendment to the protocol and the Statistical Analysis Plan will detail how data will be handled in the primary analysis. (revised per Amendments 02 and 04)

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

At the conclusion of the study, all unused drug supplies are to be returned to the Eisai approved contract packaging vendor.

### 9.4.7 Prior and Concomitant Therapy

Medication (including over-the-counter medications) or therapy administered to the subject before the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs during the Core Study and OLE Phase are provided in Appendix 2. (revised per Amendment 07) Prohibited medications are presented in Listing 1 through Listing 5. Medications that are permitted with restrictions are listed in Listing 6 through Listing 8. (revised per Amendment 04)

The types of agents listed below are not permitted before randomization unless discontinued according to the specific timeframes as shown below; these types of agents are not permitted during the Core Study or OLE Phase until after the last treatment visit: (revised per Amendments 04 and 07)

- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines

- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization. However, during the treatment period of the study, short term (not more than 14 days) use of steroids up to the equivalent of prednisolone 40 mg once daily is permitted after discussion with the Medical Monitor. Dosing with study drug should be suspended from the time steroid treatment is started. Complete blood count and lymphocyte subsets should be determined prior to starting steroid treatment and continue to be monitored weekly. Study drug may be resumed after discussion with the Medical Monitor when the following conditions are met: (1) treatment with steroids has been completed for at least 1 week; (2) absolute lymphocytes not <LLN; (revised per Amendments 07) (3) no lymphocyte subsets are below the discontinuation threshold (for Core Study only); (4) the investigator considers that the medical condition which required treatment with steroids has improved or resolved. Weekly testing of lymphocyte subset counts (for Core Study only) and CBC with differentials is required for 4 weeks following resumption of study drug administration. (revised per Amendment 04)
- (revised per Amendment 06)

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for any efficacy analyses. (revised per Amendment 05)

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed. Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before randomization. They may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 04)
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety, and are not prohibited above. (revised per Amendment 05)

Antiplatelet therapy: (revised per Amendment 04)

- For subjects who consent to CSF sample collection: Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) are permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also

permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

- For subjects who do not consent to CSF sample collection: Aspirin and clopidogrel, individually or in combination, are permitted.

### 9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period. CRAs will review treatment compliance during site visits and at the completion of the study.

### 9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the principal investigator including a copy of the principal investigator's current medical license (required for United States sites) or medical registration number on the curriculum vitae
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

## 9.5 Study Assessments

### 9.5.1 Assessments

#### 9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

#### 9.5.1.2 Baseline Assessments

Assessments to be made at Screening and Baseline and throughout the study are described in Section 9.5.1.3, Section 9.5.1.4, and Section 9.5.1.5.

##### 9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, current medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment due to AD. Subjects will be asked about history of TB, infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV Types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include onset, duration, relapse frequency, severity, and treatments. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The 15-item GDS and modified Hachinski ischemic scale will also be assessed at Screening as part of the exclusion criteria.

Physical examinations (complete or routine) will be performed as designated in Table 6, Table 7, and Table 14. (revised per Amendment 07) A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, and skin, and a neurological examination (including the Brief Smell Identification Test [Sensonics Inc.]). (revised per Amendment 04). A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

##### 9.5.1.2.2 VIRAL TESTING

As specified in Table 6, blood will be collected for screening for Hepatitis B and Hepatitis C for determining eligibility, and at Baseline for viral characterization.

##### 9.5.1.2.3 B12 TESTING

Blood will also be collected for vitamin B12 levels as specified in Table 6.

#### 9.5.1.2.4 TB EXPOSURE TESTING

Blood will also be collected for testing for previous TB exposure, as specified in Table 6.

#### 9.5.1.2.5 URINE DRUG TESTING

Urine will be collected for drug screening as specified in Table 6.

### 9.5.1.3 Efficacy Assessments

#### 9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

The timing of psychometric assessments is shown in Table 6, Table 7, and Table 14. (revised per Amendment 07) These assessments should be administered in the morning (or, if not possible, consistently at the same time of day) and should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). At the Screening Visit, the recommended order of assessments is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. At the Baseline Visit, the assessments are to be conducted in the following order: MMSE, CDR, ADAS-cog$_{14}$, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). (revised per Amendment 02)

At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

**Alzheimer's Disease Assessment Scale - cognitive subscale:** Discussed in Section 9.2.3. (revised per Amendment 05)

**Clinical Dementia Rating:** The CDR assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

**Mini Mental State Examination:** A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

**ISLT:** The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects will read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 15 minutes, in which time the CBB is performed, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

**CogState Brief Battery:** The CBB is a computer-based battery comprising 4 cognitive tests:

- Detection – a simple reaction time test where the subject presses a key when the card is turned face up from a pack of cards ("Has the card turned over"). Speed of response is the measure.
- Identification – a simple choice reaction time test where the subject presses 1 of 2 keys when the card just turned face up is either a red card or a black card ("Is the card red"). Speed of response is the measure.
- One Card Back – a simple working memory test where the subject presses 1 of 2 keys when the card turned face up is either the card seen in the immediately previous trial or not ("Is the previous card the same"). Accuracy of response is the measure.
- One Card Learning – a visual learning and memory test where the subject presses 1 of 2 keys depending on whether the card just turned face up has been seen before or not in the task ("Have you seen this card before in this task"). Accuracy of response is the measure.

**Functional Assessment Questionnaire:** The caregiver or informant provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent). (revised per Amendment 04)

#### 9.5.1.3.2 VOLUMETRIC MRI

Volumetric MRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the Alzheimer's Disease Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

Volumetric MRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. Volumetric MRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. Volumetric MRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 6, Table 7, and Table 14 according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. (revised per Amendment 07) Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

For subjects who consent to CSF sample collection, CSF samples will be collected by LP (gravity drip method) at the timepoints specified in Table 6 and Table 7 (revised per Amendment 02). The CSF sample taken at the Baseline Visit will only be performed after subjects consent to CSF sample collection, and after confirmation of an amyloid positive PET scan (revised per Amendment 02). See Section 9.5.1.4.2 for further details.

### 9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

#### 9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609). For subjects who consent to CSF sample collection, CSF samples will be collected for the determination of elenbecestat (E2609) concentrations. (revised per Amendment 02) Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with elenbecestat (E2609).

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 6 and Table 7. Two PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visits 5, 11, 14, and 16, and 4 to 8 hours postdose at Visit 7 and Visit 18 (or at the ED Visit). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug with food at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or at the ED Visit) the PK blood sample should be collected shortly before or shortly after completing the LP. (revised per Amendment 01) Although the PK sampling procedures at the ED visit should follow those of Visit 18, in the event that study drug has already been discontinued prior to the ED visit, then no dosing will be conducted. However, a PK sample at trough (before LP) will be collected, followed by LP at approximately the same time as previous visits. A 2nd PK blood sample will be collected as close as possible in time to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

Blood will also be drawn where possible at the 1st report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

#### 9.5.1.4.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

**Biomarkers**

Subjects who consent to CSF sample collection will be encouraged to stay at the site after completion of LP for medical observation (revised per Amendment 02). At Baseline, a CSF sample will be collected by LP (gravity drip method) after fasting (preferred), or at least 2 hours after the most recent meal (Section 9.5.1.3.3). The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 [or later postrandomization timepoint] and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. (revised per Amendment 04) At visits where cognitive tests are also performed, if the tests are to be performed on the same day, the LP must be performed after the cognitive tests have been completed and the subjects should rest and drink some fluid to hydrate before the LP. (revised per Amendment 01) The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. The CSF sample will be used for PD assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 levels and activity. (revised per Amendment 04)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to

postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The pre- and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendment 04) BACE1 levels will be measured using internally developed fluorescence resonance energy transfer and ELISA based assay(s). Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

The blood sample collected for PD analyses at Baseline should be collected on the same day shortly before or shortly after completing the LP at Baseline. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

At the Baseline Visit, blood samples will be collected and stored for determination of prior exposure to any suspected infective agents in the event that the subject develops treatment-emergent AEs that warrant further investigation (eg, treatment-emergent infection). For subjects who consented to CSF sample collection, CSF samples from the Baseline Visit will also be stored for the same purpose. (revised per Amendment 02) Testing may include, but not be limited to, serological tests, viral titer by quantitative polymerase chain reaction, or human leukocyte antigen genotyping.

Blood samples will be collected for PD assessments as specified in Table 6, Table 7, and Table 14. (revised per Amendment 07)

For all subjects, baseline and on-study blood samples, DNA samples, and any CSF samples collected from subjects who consent to CSF collection will be stored for up to 15 years. (revised per Amendment 02)

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

**Pharmacogenomics**

A blood sample will be obtained at Baseline and will be used to determine the *ApoE* genotype (homozygous or heterozygous E4 versus non-E4) and the *NAT2* phenotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response, safety, or PK of elenbecestat (E2609). Details of which genotype/phenotype data will be applied to the analyses of efficacy, safety or PK will be discussed in the Statistical Analysis Plan.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the

development of AEs, or underlying AD. Variations in elenbecestat (E2609) exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

**Amyloid PET**

An amyloid PET scan will be performed at Screening to confirm deposition of amyloid in the brain. An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02) Longitudinal amyloid PET imaging will also be conducted after 18 months of Core Study treatment (or at the Core Study ED Visit if the subject has received study drug for at least 39 weeks). (revised per Amendment 07) Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses) (Table 6). (revised per Amendments 02 and 05) PET scanning will be performed with a locally approved Aβ imaging agent (eg, Amyvid). Descriptions and detailed instructions for all imaging can be found in the imaging manual.

Amyloid PET imaging is an exploratory measure of the potential disease-modifying effects of elenbecestat (E2609).

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, lymphocyte subsets, Igs, and urine values; periodic measurement of vital signs and ECGs; performance of physical and neurological examinations; centralized dermatological assessments; the C-SSRS; and safety MRIs as detailed in Table 6, Table 7, and Table 14 will also be conducted. (revised per Amendment 07) Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and posttreatment for exploratory immunomodulatory and immune-based analyses.

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (see Section 9.4.6). (revised per Amendment 01)

##### 9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is elenbecestat (E2609).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: It is not necessary to report every sign or symptom as a separate AE if the overall disease [diagnosis] is being reported as an AE.)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, discontinuation of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit during the Core Study (Visit 20, as shown in Table 7, for subjects who do not enter the OLE Phase) or the last Visit during the OLE Phase (Visit 34 as shown in Table 14, for subjects who participate in the OLE Phase). (revised per Amendment 07) Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF. SAEs will be collected for 3 months after the last dose of study drug, (ie, through to the final Follow-Up visit [Visit 20 for subjects who do not enter the OLE Phase or Visit 34 for subjects who participate in the OLE Phase]). (revised per Amendments 04, 05, and 07)

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the ADAS-cog$_{14}$, MMSE, ISLT and CBB (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 4.

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis
- Dissociative state

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.11 for a description of the C-SSRS).

The following AEs will require the collection of information sufficient to provide a detailed description of the event, treatment and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection; any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a "yes" answer to Type 4 or 5 suicidal ideation, or a "yes" response to any suicidal behavior on the C-SSRS.

All AEs must be followed through the final Follow-Up visit (Visit 20 for subjects who do not enter the OLE Phase or Visit 34 for subjects who participate in the OLE Phase), or until resolution, whichever comes first. (revised per Amendment 07) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. (revised per Amendment 04)

**Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.**

### Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

### Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

*Classification of Causality*

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

#### 9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reportable using the criteria of important medical event if the event does not meet other serious criteria: new onset seizures, ocular herpes.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the eCRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

#### 9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 4. Subjects should be in a seated or supine position during blood collection. Table 6, Table 7, and Table 14 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study. (revised per Amendment 07)

See Section 9.3.3 and Appendix 6 for safety criteria for discontinuation from study drug-related to absolute counts of CD4, CD8, and B lymphocytes, and for lymphocyte subset counts.

## Table 4 Clinical Laboratory Tests

| Category | Parameters |
|---|---|
| **Hematology** | Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils).<br><br>PT, PTT, and INR (Screening, Baseline, and Visit 21 only) (revised per Amendment 02 and 07) |
| **Chemistry** | |
| **Electrolytes** | Bicarbonate, calcium, chloride, phosphate, potassium, sodium |
| **Liver function tests** | Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin |
| **Renal function tests** | Blood urea/blood urea nitrogen, creatinine |
| **Other** | Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid |
| **Urinalysis** | Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells |
| **Other** | Lymphocyte T and B cell subset analyses (see Table 5). Regulatory T cells (revised per Amendment 04)<br>PBMCs (revised per Amendment 02)<br>Ig analyses (IgG, IgA, and IgM).<br>Viral screen (HCVAb [Hepatitis C] and HbsAg [Hepatitis B]).<br>Viral characterization (including HSV1, HSV2 and CMV, etc)<br>Serum pregnancy test (females of child bearing potential only)<br>Tuberculosis Interferon Gamma Release Assays<br>Tests for thyroid function (thyroid stimulating hormone, free triidothyronine and free thyroxine) and vitamin B12<br>Blood sample for storage for subsequent testing of immune status<br>Cerebrospinal fluid sampling |

Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials must also be repeated. (revised per Amendment 02)

CMV = cytomegalovirus, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV = herpes simplex virus, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PT = prothrombin time, PTT = partial thromboplastin time.

The 8 different surface markers (including but not limited to CD3, CD4, CD8, CD45, CD19, CD16, CD56, and CD14) and absolute lymphocyte counts will be measured in order to provide the lymphocyte subset data as shown in Table 5. In addition, Regulatory T cells will be measured. Current sponsor data supports the literature showing there is an age-related decline in lymphocyte subsets (see Appendix 5). These data have been used to revise the LLNs for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts to the population-adjusted LLNs of 396, 157, and 74 cells/µL, respectively) (revised per Amendments 02 and 04).

**Table 5 Lymphocyte Subtypes Inclusive in BD Trucount™**

| Cell Type | Cell Surface Markers |
|---|---|
| T lymphocytes | CD3 |
| T helper cells | CD3+, CD4 |
| Cytotoxic T cells | CD3+, CD8 |
| Mature B cells | CD3-, CD19 |
| Natural killer cells | CD3-, CD16, CD56 |
| Macrophages | CD14 |

(Table 5 revised per Amendment 04)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the case report form [CRF] Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

#### 9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [bpm], respiratory rate [per minute], body temperature [in centigrade], and weight [kg]) will be obtained at the visits designated in Table 6, Table 7, and Table 14 by a validated method. (revised per Amendment 07) Measurements of sitting BP and heart rate will be obtained. All BP measurements should be performed on the same arm, preferably by the same person.

#### 9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination will be performed at Screening as described in Section 9.5.1.2.1. At Baseline and during the Randomization Phase, routine physical examinations will take place as shown in Table 7 and Table 14. (revised per Amendment 07) These examinations will include the cardiovascular system, respiratory system, and neurological system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 6, Table 7, and Table 14. (revised per Amendment 07) During the Core Study, twelve-lead standard ECGs will be

recorded in triplicate (1 minute apart) after subjects have been resting in the supine position for at least 5 minutes. During the OLE Phase, a single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12 lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. (revised per Amendment 07)

On any study day when ECG, vital signs, and blood samples are taken, these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.7 SAFETY MRI

Safety brain MRI assessments will be performed at the times shown in Table 6, Table 7, and Table 14. (revised per Amendment 07) Additional safety MRI scans can be performed at unscheduled visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Safety MRIs will be acquired using a standardized procedure that will include fluid-attenuated inversion recovery (FLAIR), gradient-echo, T1, and diffusion-weighted sequences to determine the presence of focal lesions including, but not limited to, evidence for ischemic and hemorrhagic stroke, subdural hematoma, neoplasm, arteriovenous malformation, micro and macrohemorrhages, superficial siderosis, lacunar infarcts, white matter abnormalities, and vasogenic edema. The imaging sequence for the Screening/safety MRI will include: T2 weighted anatomic MRI to rule out major white matter changes, cerebral infarction or other structural lesions, and a high-resolution 3D T1-weighted scan with isotropic voxels with volumes of 1 $mm^3$ or less. In addition, both FLAIR for the detection of vasogenic edema and T2 Gradient Recall Echo for the detection of microhemorrhages will be acquired. The 3D dataset will be reconstructed in transverse slices in Digital Imaging and Communications in Medicine format. The results of this MRI assessment will also be used as the Baseline Period MRI, against which changes after drug administration will be compared. Further details of the MRI protocol can be found in the Imaging Acquisition Guideline. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, 18, 20, and 32. (revised per Amendments 04 and 07) In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

At any time during the treatment period, subjects will be discontinued from study drug if they develop any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. All of these features must be reported as study specific AEs (or AEs of special interest). These subjects will undergo an ED Visit within 7 days after study drug discontinuation; as well as 4 Follow-Up Visits at 2, 4, 8 and 12 weeks after the last dose of Core Study treatment or 2 Follow-Up Visits at 4 and 12 weeks after the last dose of OLE treatment. (revised per Amendments 04 and 07) Subjects will also undertake an Unscheduled Visit (with MRI) at approximately 30 days after the visit at which such MRI features were first identified. Additional visits may be arranged if clinically indicated in the opinion of the investigator, and may occur later than 12 weeks after the final dose of study drug.

#### 9.5.1.5.8 DERMATOLOGIC ASSESSMENT

During the Core Study, centralized skin assessments, using standardized photography, will be performed by a reviewing dermatologist at the times shown in Table 6 and Table 7. During the OLE Phase, all dermatologic assessments will be performed by the investigator at the times shown in Table 14. (revised per Amendment 07) All assessments will specifically include evaluation of any areas of depigmentation or any rash.

In addition, subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregiver or informants will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or infection, and the investigator will be required to review such AEs as soon as possible and consider an unscheduled physical and dermatological evaluation. Detailed characteristics of any skin rashes will be captured in the clinical database. Physical examination may be undertaken where indicated. Treatment-emergent abnormal dermatological findings should be reported as AEs.

#### 9.5.1.5.9 NEUROLOGIC EXAMINATION

Neurological examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations as shown in Table 6, Table 7, and Table 14. (revised per Amendment 07) Details of these examinations will be captured in an eCRF. The neurological examinations will monitor for new symptoms and signs which will then alert the investigator to consider new CNS pathology (especially slowly-evolving neurological conditions that may not lead to prominent symptoms). Examples of neurological signs that may indicate new CNS pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. In such a situation, the investigator should consider (but not limited to) demyelination in the differential diagnoses, and should discuss with the sponsor's medical monitor further

investigations or treatment, which will be decided case by case. Neurological examinations will also include the assessment of cranial nerve function, especially the olfactory nerve; the Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits to objectively test olfaction. Treatment-emergent abnormal neurological findings should be reported as AEs.

#### 9.5.1.5.10 PREGNANCY TEST

At Screening and Visit 21, females of childbearing potential will have a serum pregnancy test. At Baseline and during the Treatment Period, urine samples will be obtained from females of childbearing potential for pregnancy tests (see Table 7 and Table 14). (revised per Amendment 07)

#### 9.5.1.5.11 COLUMBIA SUICIDE SEVERITY RATING SCALE

An assessment of suicidal ideation and behavior using the C-SSRS will be performed at the designed time points in Table 6, Table 7 and Table 14. (revised per Amendment 07) A "yes" answer to Type 4 or 5 suicidal ideation or a "yes" response to any suicidal behavior queries will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

#### 9.5.1.5.12 BIOMARKER SAMPLES

As noted in Section 9.5.1.4.2, CSF (for subjects who consent to CSF sample collection), blood, and DNA samples will be collected and may be used for exploratory biomarker analyses, as well as tested in the event that a subject develops AEs that warrant further investigation. (revised per Amendment 02)

#### 9.5.1.5.13 OPHTHALMIC EXAMINATIONS

An ophthalmic examination will be conducted at Baseline (unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available). An additional examination will be conducted, if the subject experiences visual disturbances during the course of the study or is medically indicated. The ophthalmic examinations should include fundoscopy to look at the optic disc, macula and the rest of the retina, as well as an assessment of visual acuity and visual fields.

### 9.5.2 Schedule of Procedures/Assessments

The Schedule of Procedures/Assessment is described in this section for the Core Study only. The Schedule of Procedures/Assessment for the OLE Phase is provided in Appendix 6, Table 14. (revised per Amendment 07)

### 9.5.2.1 Schedule of Procedures/Assessments

Table 6 presents the Schedule of Procedures/Assessments for the Core Study Prerandomization Phase. Screening assessments will be organized into 4 tiers (see below and Figure 2). Table 7 presents the Schedule of Procedures/Assessments for the Core Study Randomization Phase.

**Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)**

| Phase | Prerandomization | |
|---|---|---|
| Period | Screening | Baseline |
| Visit | 1 | 2 |
| **Procedures/Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)** | | |
| Informed consent (subject and caregiver or informant) | X (Tier 1) | |
| Subject informed consent for CSF sample collection (voluntary)[a] | X | X |
| Demographics | X (Tier 1) | |
| Medical history[b] | X (Tier 1) | |
| Prior/concomitant medications[c] | X (Tier 1) | X |
| Vital signs including weight[d] | X (Tier 1) | X |
| Height | X (Tier 1) | |
| Complete physical examination | X (Tier 1) | |
| Routine physical examination | | X |
| CBB and ISLT[e] | X (Tier 1) | X |
| MMSE[e] | X (Tier 1) | X |
| CDR[e] | X (Tier 1) | X |
| FAQ[e] | X (Tier 1) | X |
| ADAS-cog$_{14}$[e] | | X |
| 15-item Geriatric Depression Scale | X (Tier 2) | |
| Modified Hachinski ischemic scale | X (Tier 2) | |
| C-SSRS | X (Tier 2) | X |
| 12-lead ECG[f] | X (Tier 2) | X |
| Blood and urine for clinical laboratory tests[g] | X (Tier 2) | X |
| Blood for lymphocyte subset analyses[h] | X (Tier 2) | X |
| Blood for Ig analyses[i] | X (Tier 2) | X |
| Blood for viral screen[j] | X (Tier 2) | |
| Blood for thyroid function tests[k] | X (Tier 2) | |
| Blood for vitamin B12 test | X (Tier 2) | |
| Test for previous TB exposure | X (Tier 2) | |
| Urine drug screen | X (Tier 2) | |
| Serum pregnancy test (females of childbearing potential only) | X (Tier 2) | |
| Urine pregnancy test (females of childbearing potential only) | | X |
| Safety and Volumetric MRI[l] | X (Tier 3) | |
| Amyloid PET scan[m] | X (Tier 4) | |
| Inclusion and Exclusion criteria | X (All tiers) | X |
| Adverse events | X (All tiers) | X |
| CSF sampling for PK, PD and storage[a] | | X |
| Blood sample for PK assessments[n] | | X |
| Blood sample for PD and exploratory biomarker assessments[o] | | X |
| Blood sample for pharmacogenomics | | X |

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

| Phase | Prerandomization | |
|---|---|---|
| Period | Screening | Baseline |
| Visit | 1 | 2 |
| **Procedures/Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)** | | |
| Blood sample for storage for immune status[p] | | X |
| Blood sample for PBMC isolation | | X |
| Blood sample for viral characterization[q] | | X |
| Centralized dermatological assessment via photography[r] | | X |
| Neurological examinations[s] | | X |
| Ophthalmic assessment[t] | | X |

(Table revised per Amendments 02 and 04)

AChEI = acetylcholinesterase inhibitor, AD = Alzheimer's disease, ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CDR = Clinical Dementia Rating, CMV = cytomegalovirus, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), Ig = immunoglobulin, INR = International Normalized Ratio, ISLT = International Shopping List Task (immediate and delayed recall), LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetics, PET = positron emission tomography, PT = prothrombin time, PTT = partial thromboplastin time, TB = tuberculosis.

Note: Screening assessments/procedures have been organized into 4 distinct tiers. All assessments and procedures in each tier should be completed (see Figure 2), and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures, as long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. Similarly, all screening assessments and procedures must be completed, and eligibility to continue in the study confirmed, before any baseline assessments and procedures commence. Adverse events and eligibility against inclusion and exclusion criteria must be assessed at each stage within the Screening Visit and at the Baseline Visit. (revised per Amendment 01)

Note: All screening and baseline assessments are to be completed within 50 days, plus an additional window of up to 30 days if required (revised per Amendment 02). The interval between availability of the results of the last screening assessment (PET scan) and the first baseline (Visit 2) assessments should be as short as possible and ideally should not exceed 7 days. Visit 3 (Randomization) (see Table 7) should occur no more than 10 days after completion of the Baseline visit (Visit 2) and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion No.20 into account (revised per Amendment 02). Thus, the total Prerandomization Phase may be up to 60 days, plus an additional window of up to 30 days if required (revised per Amendment 02).

a: Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. For those subjects who do consent to CSF sample collection: CSF will be collected by LP after fasting (preferred), or at least 2 hours after the most recent meal. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 [or later postrandomization timepoint] and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. If the LP and cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. The CSF sample will be used for PK and PD assessments. A CSF sample will also be stored for testing in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). (revised per Amendments 01, 02, and 04)

b: To include: mild cognitive impairment and AD history; history of TB, vaccination history against and infections due to varicella zoster virus (chickenpox and herpes zoster or shingles); infections due to HSV1 (orolabial herpes or cold sores) and 2 (genital herpes). Medical history of infections to include: onset, duration, relapse frequency, severity, and

treatments. For any active infection within the last 4 weeks prior to randomization, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)

c: Prior and concomitant medications include AChEIs and memantine, and other medications for cognitive decline.

d: Weight, respiratory rate, body temperature, and sitting blood pressure and heart rate will be obtained.

e: To be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). At the Screening Visit, the recommended order of assessments is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. At the Baseline Visit, the assessments are to be conducted in the following order: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). (revised per Amendment 02) At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

f: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

g: Clinical laboratory tests consist of hematology (including PT, PTT, and INR), clinical chemistry, and urinalysis.

h: Lymphocyte subsets will include but are not limited to the following cell surface marker assessments: CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cells), CD16/CD56 (natural killer cells) and CD14 (macrophages). Regulatory T cells will also be measured. Viability staining may also be employed. Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials, must also be repeated. (revised per Amendments 02 and 04)

i: Igs to be analyzed include IgG, IgA and IgM.

j: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

k: Thyroid function tests include thyroid stimulating hormone, free triidothyronine, and free thyroxine.

l: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images. MRI will be read by an approved central reader. Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session. (revised per Amendment 01)

m: PET scanning will be performed with a locally approved β-amyloid imaging agent, eg, Amyvid if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. The PET image will be centrally read for the purpose of determining eligibility for inclusion into the study. An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02)

n: The PK blood sample should be collected on the same day shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

o: The PD and exploratory biomarker blood sample should be collected shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

p: A blood sample will be collected at Baseline and stored. This sample may be used for exploratory biomarkers associated with study drug or disease, or in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

q: Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

r: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. See Section 9.5.1.5.8 for further details.

s: To be performed by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. Section 9.5.1.5.9 details what is included in the neurological examination. The Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits and serves as part of the neurological examination. (revised per Amendment 04)

t: An ophthalmic examination will be conducted at Visit 2 unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available. The ophthalmic examination should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| Phase | Randomization | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Period | Treatment | | | | | | | | | | | | | | | | | Follow-Up | | | | | |
| Visit[a] | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | ED[b] | W2 | 19[c] | W8 | 20[c] | UNS Visit[d] | Interim Safety Visit |
| Day | 1 | 8 | 15 | 22 | 29 | 43 | 57 | 71 | 85 | 113 | 141 | 183 | 274 | 365 | 456 | 547 | | 561 | 575 | 589 | 631 | | |
| Week | 1 | 2 | 3 | 4 | 5 | 7 | 9 | 11 | 13 | 17 | 21 | 27 | 40 | 53 | 66 | 79 | | 81 | 83 | 87 | 91 | | |
| Weeks elapsed since first dose | 0 | 1 | 2 | 3 | 4 | 6 | 8 | 10 | 12 | 16 | 20 | 26 | 39 | 52 | 65 | 78 | | 80 | 82 | 86 | 90 | | |
| Nominal months elapsed since first dose | 0 | | | | 1 | | 2 | | 3 | 4 | 5 | 6 | 9 | 12 | 15 | 18 | | | 19 | | 21 | | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | | | | |
| Routine physical examination | X | | | | X | | X | | X | | | X | X | X | X | X | X | | X | | X[e] | X | |
| Inclusion and Exclusion criteria | X | | | | | | | | | | | | | | | | | | | | | | |
| Vital signs[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X[e] | X | X |
| Respiratory rate | | | | | X | | X | | X | X | X | X | X | X | X | X | X | | X | | X[e] | X | |
| Weight | | | | | | | | | X | | | X | X | X | X | X | X | | | | X | X | |
| Centralized dermatological assessment via photography[g] | | | | | | | | | X | | | X | X | X | X | X | X | | | | X | X | |
| Neurological examination[h] | | | | | | | | | | | | X | | X | | X | X | | X | | X | X | |
| Ophthalmic examination[i] | | | | | | | | | | | | | | | | | | | | | | X | |
| Concomitant medications[j] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | X | X |
| 12-lead ECG[k] | | | X | | X | | X | | X | | | X | | X | | X | X | | X | | X[e] | X | |
| Clinical biochemistry and urinalysis | | | X | | X | | X | | X | | | X | X | X | X | X | X | | X | | X | X | |
| Complete blood count | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[l] | X |
| Blood samples (lymphocyte subset analyses)[l] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[l] | X |
| Blood samples (Igs)[m] | | | | | X | | X | | X | | | X | | X | | X | X | | X | X | X | X | |
| Blood samples (isolation of PBMCs) | | | X | | | | | | X | | | | | | | | | | | | X | | |
| Urine pregnancy test (females of CBP only) | X[n] | | | | | | | | X | | | X | X | X | X | X | X | | X | | | X | |
| Blood sample (storage for immune status)[o] | | | | | X | | | | X | | | X | | X | | X | X | | X | | X | X | |
| CBB and ISLT[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | | |
| MMSE[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | | |
| CDR[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | | |
| ADAS-cog$_{14}$[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | | |

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| **Phase** | **Randomization** | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | | | | | **Follow-Up** | | | | | |
| **Visit[a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **ED[b]** | **W2** | **19[c]** | **W8** | **20[c]** | **UNS Visit[d]** | **Interim Safety Visit** |
| **Day** | **1** | **8** | **15** | **22** | **29** | **43** | **57** | **71** | **85** | **113** | **141** | **183** | **274** | **365** | **456** | **547** | | **561** | **575** | **589** | **631** | | |
| **Week** | **1** | **2** | **3** | **4** | **5** | **7** | **9** | **11** | **13** | **17** | **21** | **27** | **40** | **53** | **66** | **79** | | **81** | **83** | **87** | **91** | | |
| **Weeks elapsed since first dose** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **10** | **12** | **16** | **20** | **26** | **39** | **52** | **65** | **78** | | **80** | **82** | **86** | **90** | | |
| **Nominal months elapsed since first dose** | **0** | | | | **1** | | **2** | | **3** | **4** | **5** | **6** | **9** | **12** | **15** | **18** | | | **19** | | **21** | | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | | | | |
| FAQ[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | | |
| C-SSRS | | | | | X | | X | | X | | | X | X | X | X | X | X | | X | | X[e] | X | |
| Safety and Volumetric MRI[q] | | | | | | | | | | | | X | | X | | X | X | | | | X | X | |
| Amyloid PET[r] | | | | | | | | | | | | | | | | X | X | | | | | | |
| Telephone contact[s] | | | X | | X | | | | X | | | X | | X | | X | X | | | | | X | |
| Blood samples for PK[t] | | | X | | X | | | | X | | | X | | X | | X | X | | | | | X | |
| Blood samples for PD and exploratory biomarkers[u] | | | X | | X | | | | X | | | X | | X | | X | X | | X | | X | | |
| CSF sampling for PK and PD[v] | | | | | X | | | | | | | | | | | X | X | | | | | X | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[l] | X |
| Sleep/dream questionnaire[w] | | | | | | | | | | | | | | | | | | | | | | X | |
| Randomization | X | | | | | | | | | | | | | | | | | | | | | | |
| Dispense study drug[x] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | | | |

**Footnotes for Table 7**

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating scale, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), Ig = immunoglobulin, ISLT = International Shopping List Task, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, UNS = unscheduled, W2 = new Week 2 follow-up visit, W8 = new Week 8 follow-up visit. (revised per Amendment 04)

a: Visit 3 should be conducted no more than 10 days after completion of the Baseline visit (Visit 2) assessments and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion #20 into account. (revised per Amendment 02) A window of ±3 days will be permitted for Visit 4 to 14 inclusive. A window of ±10 days will be permitted for Visit 15 to 18 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since first dose" at subsequent visits.

b: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug (Visit W2, 19, W8, and Visit 20, respectively). (revised per Amendments 04 and 05)

c: All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 4 posttreatment Follow-Up visits; 2, 4, 8, and 12 weeks after the last dose of study drug (Visits W2, 19, W8, and 20, respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up period. (revised per Amendment 04)

d: Unscheduled visits may be conducted at any time that safety or safety MRI data indicate per protocol or as clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

e: Only if clinically significant abnormalities are found at Visit 19 and the investigator considers it necessary to repeat at Visit 20. Clinical biochemistry, urinalysis, CBC, lymphocyte subsets and Igs should always be performed at Visit 20, regardless of clinical significance at the previous Follow-Up visit. (revised per Amendments 02 and 04)

f: Measurements of body temperature and sitting blood pressure and heart rate will be obtained.

g: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. Additional UNS dermatological assessments should be conducted in response to any dermatological AEs of concern (eg, depigmentation, rash, herpetic lesion).

h: Examples of neurological signs that may indicate new central nervous system pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. The Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits and serves as part of the neurologic examination. (revised per Amendment 04)

i: If the subject experiences visual disturbances during the course of the study, the subject will be referred to a specialist for a further ophthalmic examination, which should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields

j: Please refer to Section 9.4.7, which details prohibited and permitted medications in the study and associated timeframes.

k: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

l: Lymphocyte subsets will include but are not limited to the following cell surface marker assessments: CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [NK cells] and CD14 [macrophages]) and absolute lymphocytes. Regulatory T cells will also be measured. Viability staining may also be employed. Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a Complete Blood Count, with differentials, must also be performed along with assessment of AEs. (revised per Amendments 02 and 04)

**Footnotes for Table 7**

m: Igs to be analyzed include IgG, IgA, and IgM.

n: An additional assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

o: Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops a TEAE that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

p: These assessments are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The order of assessments will be: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). At visits where the CDR or FAQ are conducted, the investigator will determine whether the informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

q: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images in MRI will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, 18, and 20. In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A volumetric MRI sequence will be collected in all subjects immediately following all safety MRI assessments. (revised per Amendment 01)

r: PET scanning will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks. A PET scan will only be performed at Visit 18 or ED if the subject has a valid Screening PET scan for the purposes of longitudinal analyses; subjects who were determined to be eligible for the study on the basis of an historical PET scan will not have a PET scan performed at Visit 18 or ED (revised per Amendment 02)

s: Site staff will contact the subject or the caregiver or informant the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the caregiver or informant, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

t: Two plasma PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visit 5, Visit 11, Visit 14, and Visit 16 and 4 to 8 hours postdose at Visit 7 and Visit 18 (or ED). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or ED) the PK blood sample should be collected shortly before or shortly after completing the LP. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected, followed by LP at approximately the same time as at previous visits. A second PK blood sample will be collected as close as possible to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

u: PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day. At Visits 5, 11, 14, and 16 the PD blood samples should be collected predose.

v: For subjects who consent to CSF sample collection: Postrandomization CSF sample collection is scheduled at Visit 7 (or later postrandomization timepoint) and Visit 18/ED. If a postrandomization CSF sample is collected later than Visit 7, time-matched plasma PK samples are also required (see Footnote t). All visits at which CSF samples are scheduled to be taken also include blood PK and PD assessments and so the subject will be dosed at the clinic on these days. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 [or later postrandomization timepoint] and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If the LP and the cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already

**Footnotes for Table 7**

stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. . Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendments 01, 02, and 04)

w: Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

x: The first dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time as determined by the PI or Safety Physician for postdose medical observation. (revised per Amendment 02)

#### 9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 6 and Table 7 for the timings of the procedures and assessments to be performed during the Core Study. Screening assessments will be organized into 4 tiers (see Table 6, Section 9.5.2, and Figure 2. (Revised per amendment 07)

See Section 9.5 for a full description of the procedures and assessments to be performed during this study.

Table 8 presents the number of blood and CSF samples, and the total volume of blood and CSF that will be collected throughout the Core Study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety. (Revised per amendment 07)

**Table 8 Summary of Blood and CSF Sample Volumes**

| Assessment | Total number of collection time points | Number of time points × volume per collection (mL whole blood or CSF) | | Total volume (mL whole blood or CSF) |
|---|---|---|---|---|
| | | Screening and Baseline Periods | Treatment and Follow-up Periods | |
| **Blood** | | | | |
| Chemistry | 12 | 2 × 2 mL | 10 × 2 mL | 24 mL |
| Hematology | 20 | 2 × 5 mL | 18 × 5 mL | 100 mL |
| Lymphocyte subset analyses[a] | 20 | 2 × 4 mL | 18 × 4 mL | 80 mL |
| PBMC | 4 | 1 × 16 mL | 3 × 16 mL | 64 mL |
| IgA, IgM, IgG | 10 | 2 × 2 mL | 8 × 2 mL | 20 mL |
| PT, PTT for INR | 2 | 2 × 3 mL | None | 6 mL |
| Thyroid function tests (thyroid stimulating hormone, free triidothyronine and free thyroxine) | 1 | 1 × 3 mL | None | 3 mL |
| Viral screen (Hepatitis B and C) | 1 | 1 × 4 mL | None | 4 mL |
| Viral characterization | 1 | 1 × 4 mL | None | 4 mL |
| Vitamin B12 | 1 | 1 × 2 mL | None | 2 mL |
| Serum pregnancy test | 1 | 1 × 2 mL | None | 2 mL |
| Tuberculosis (interferon-gamma release assays) | 1 | 1 × 3 mL | None | 3 mL |
| Sample for immune status | 8 | 1 × 4 mL | 7 × 4 mL | 32 mL |
| PD sample | 9 | 1 × 4 mL | 8 × 4 mL | 36 mL |
| PK analysis | 7 | 1 × 3 mL | 6 × 6 mL | 39 mL |
| Pharmacogenetic sample | 1 | 1 × 3 mL | None | 3 mL |
| All blood samples, total volume whole blood collected | | 80 mL | 342 mL | 422 mL |
| **CSF (For subjects who consent to CSF sample collection) (revised per Amendment 02)** | | | | |
| PD and PK samples | 3 | 1 × 12 mL | 2 × 12 mL | 36 mL |

CSF = cerebrospinal fluid, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetic, PT = prothrombin time, PTT = partial thromboplastin time.

a: Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials must also be performed. Therefore, for each unscheduled or repeat test, an additional 9 mL will be collected (5 mL for hematology and 4 mL for lymphocyte subset analyses)

(Table 8 revised per Amendment 04)

### 9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include vital signs, clinical laboratory assessments, physical examinations, ECG measurements, and reports of AEs. MRI will be used to detect vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage and is a standard evaluation to ensure subject safety. The C-SSRS has been endorsed by the FDA as a measure of potential suicidality (Guidance for Industry Suicidality).

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with elenbecestat (E2609), in addition to mitigating clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. Details are provided in Section 9.2.5.

### 9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

#### 9.5.4.1 Reporting of Serious Adverse Events

**All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.**

SAEs, regardless of causality assessment, must be collected up to 3 months after the last dose of study drug, ie, through to the final follow-up visit (Visit 20 for subjects who do not enter the OLE Phase or Visit 34 for subjects who participate in the OLE Phase). (revised per Amendments 04, 05, and 07) However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

**For urgent safety issues**, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

#### 9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must discontinue study treatment.

#### 9.5.4.3 Reporting of Events Associated with Special Situations

##### 9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

| | |
|---|---|
| Overdose | Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose |
| Misuse | Intentional and inappropriate use of study drug not in accordance with the protocol |
| Abuse | Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects |
| Medication error | Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject |

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

##### 9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2) should always be considered serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

#### 9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

#### 9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

#### 9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

### 9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue study drug or withdraw from the study at any time for any reason. All subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug in the Core Study (Visits W2, 19, W8, and Visit 20, respectively) or 4 and 12 weeks after the last dose of study drug in the OLE Phase (Visits 33 and 34) (see Section 9.1.2.3). (revised per Amendments 04 and 07) See Table 7 and Table 14 for full details of the assessments to be performed at these visits. (revised per Amendments 05 and 07) Subjects who discontinue study drug early (as opposed to subjects whose dosing with study drug is temporarily suspended under Medical Monitor guidance) will not be permitted to restart study drug.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and will provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who withdraw prematurely from the study will be withdrawn for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary

reason, the subject may indicate 1 or more secondary reason(s) for withdrawal from the study. Study disposition information will be collected on the Subject Disposition eCRF.

A subject removed from the study for any reason may not be replaced.

### 9.5.6 Abuse or Diversion of Study Drug

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF. (revised per Amendment 04)

### 9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

## 9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

### 9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

### 9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy assessments performed in this study.

## 9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance. (revised per Amendment 05)

### 9.7.1 Statistical and Analytical Plans

The statistical analyses of Core Study data are described in the following sections. Statistical analyses of OLE Phase data are provided in Appendix 6. (revised per Amendment 07)

Analyses will be performed based on treatment group, which will be defined in the statistical analysis plan (SAP). Additional analyses related to dose re-assignment will be performed for subjects who will be switched from elenbecestat (E2609) 5 or 15 mg to elenbecestat (E2609) 50 mg. Further details will be provided in the SAP, which will be finalized before database lock. (revised per Amendment 06)

#### 9.7.1.1 Study Endpoints

##### 9.7.1.1.1 PRIMARY ENDPOINT

- Safety and tolerability, which include incidence of TEAEs and SAEs, laboratory parameters, vital signs, and ECG parameters (revised per Amendment 05)

##### 9.7.1.1.2 SECONDARY ENDPOINTS

(revised per Amendments 02 and 05)

- % reduction of Aβ(1-x) and Aβ(1-42) in CSF relative to baseline after from 4 weeks and up to 18 months of treatment

- The population PK parameters of elenbecestat (E2609) in CSF and plasma, including the effect of intrinsic and extrinsic factors (including NAT2 phenotype) (revised per Amendment 07)

#### 9.7.1.1.3 EXPLORATORY ENDPOINTS

(revised per Amendments 01, 02, 04, and 05)

Change from baseline in:

- CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) after at least 4 weeks and at 18 months of treatment
- CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment (revised per Amendment 06)
- Total hippocampal volume at 12 and 18 months of treatment as measured by vMRI
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months of treatment as measured by vMRI
- Amyloid PET standardized uptake value ratio (SUVR) composite at 18 months for brain amyloid levels as measured
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog$_{14}$, CDR, MMSE, ISLT, CBB, and FAQ

### 9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose exploratory efficacy measurement. (revised per Amendment 05)
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration accompanied by a documented dosing history. (revised per Amendment 07)
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

#### 9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The number of randomized subjects enrolled at each site will be summarized by treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: The number (percent) of randomized and treated subjects who completed the study and who withdrew from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and withdrew from the study. The primary reasons for discontinuation from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

Completion of Study Treatment: The number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for discontinuation from the study drug are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, inadequate therapeutic response, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

#### 9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized by treatment group using descriptive statistics. Continuous demographic and baseline variables include age, MMSE and FAQ; categorical variables include sex, age group (≤65 years, age >65 years), race, ethnicity, *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal AD or mild to moderate AD). (revised per Amendment 01)

#### 9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014 or higher). (revised per Amendment 04) The number (percentage) of subjects who took prior and

concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up period will also be recorded.

#### 9.7.1.6 Efficacy and Biomarker Analyses (revised per Amendment 05)

##### 9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

There is no primary efficacy endpoint. (revised per Amendment 05)

##### 9.7.1.6.2 SECONDARY EFFICACY ANALYSES

An mixed-effects model with repeated measures (MMRM) will be used to analyze the following secondary endpoint:

- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) from 4 weeks and up to 18 months. Data from early discontinuations will also be included. (revised per Amendment 05)

##### 9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

(revised per Amendments 01, 02, 04, and 05)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months. Data from early discontinuations will also be included. (revised per Amendment 04)
- Change from baseline in CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Change from baseline in plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- Change from baseline in CSF amyloid and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment (revised per Amendment 06)
- Change from baseline in total hippocampal atrophy at 12 and 18 months as measured by vMRI
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and 18 months as measured by vMRI

- Change from baseline in Amyloid PET SUVR composite at 18 months for brain amyloid levels

The following efficacy endpoints will be summarized using descriptive statistics:

- Change from baseline in the clinical assessments: ADAS-cog$_{14}$, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months

The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

#### 9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

##### 9.7.1.7.1 PHARMACOKINETIC ANALYSES

The PK Analysis Set will be used for elenbecestat (E2609) concentration listings and for summaries of elenbecestat (E2609) concentrations in plasma and CSF by dose and day. elenbecestat (E2609) metabolite PK data may also be listed and summarized. (revised per Amendment 04)

A population PK approach will be used to characterize the plasma PK of elenbecestat (E2609). For this approach, plasma PK data from this study will be pooled with relevant data from Phase 1 studies. As appropriate, the effect of covariates on the PK of elenbecestat (E2609) will be evaluated. The PK model will be parameterized for oral clearance (CL/F) and apparent volume of distribution (Vz/F) for elenbecestat (E2609). Derived exposure parameters such as steady state area under the concentration time curve (AUC) and average concentration ($C_{avg}$) of elenbecestat (E2609) and other derived parameters will be calculated from the model using the individual estimates parameterized for oral clearance and dosing history. (revised per Amendment 04)

##### 9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Pharmacodynamic, PGx, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate statistical analysis plan. Please also refer to Appendix 3.

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). The percentage change from baseline in CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months of treatment will be analyzed and presented graphically. (revised per Amendment 05) Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status. (revised per Amendment 04)

Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels, amyloid load on PET, vMRI, and elenbecestat (E2609) dose, plasma, and CSF exposure will be initially explored graphically and any emergent relationship will be explored through population PK/PD modeling. The PK/PD relationship between plasma PK parameters with other biomarkers may also be explored using similar methods. (revised per Amendment 04)

The relationship between plasma and CSF exposure to elenbecestat (E2609) and the clinical efficacy scales (eg, MMSE, CDR) will be explored graphically. Additionally, the relationship between plasma exposures of elenbecestat (E2609) and select lymphocyte parameters will be explored graphically, and any emergent relationship will be explored using population-based modeling methods. (revised per Amendment 04)

Exposure-safety analyses may also be conducted.

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. The genomic DNA samples may also be stored and used as described in Section 9.7.1.7.2. Details of PGx testing may be provided and reported separately.

#### 9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements, and cognitive decline assessment such as CBB will be summarized by treatment group using descriptive statistics. (revised per Amendment 05)

#### 9.7.1.8.1 EXTENT OF EXPOSURE

The extent of exposure to study drug will be summarized as cumulative extent of exposure in 3-month intervals. The cumulative number and percent of subjects will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as continuous variable as well as categorical variable in 3-month intervals and the number and percent of subjects will be presented by treatment group.

#### 9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 17.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and preferred term. A subject will be counted only once within an SOC and preferred term, even if the subject experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and preferred term. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

Adverse events will be summarized by the following subgroups: *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal or mild to moderate AD). (revised per Amendment 01)

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

#### 9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

Lymphocyte subsets measured (including but not limited to CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages] and regulatory T cells) will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose.

Serum IgG, IgM, and IgA will be measured and summarized in the same manner as other laboratory parameters.

#### 9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

#### 9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to the end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 msec
- QTc interval >480 msec
- QTc interval >500 msec

Change from baseline in QTc interval:

- QTc interval increases from baseline >30 msec
- QTc interval increases from baseline >60 msec

#### 9.7.1.8.6 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include CBB (Section 9.7.1.6). (revised per Amendment 05)

### 9.7.2 Determination of Sample Size

A total of 15 subjects per dose group is deemed sufficient to derive adequate safety and PK/PD data to aid in the selection of appropriate doses and the design of the Phase 3 studies that may be planned subsequently. (revised per Amendment 05)

### 9.7.3 Interim Analysis

In order to make decisions about the remainder of the study as well as the full elenbecestat (E2609) clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. Investigators, other clinical site staff, subjects, caregivers/informants, and study team will remain blinded to study treatment. (revised per Amendments 03 and 05)

An interim safety analysis will also be conducted when all subjects have completed 12 weeks of treatment (or discontinue study drug early). (revised per Amendments 01, 03, 04, and 05)

### 9.7.4 Other Statistical/Analytical Issues

**Stratification** (revised per Amendment 01)

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

### 9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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(revised per Amendment 01)

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# 11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

## 11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

## 11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

## 11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

## 11.4 Recording of Data

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document, except when a section of the eCRF itself is used as the source document. Any correction to entries made on the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each eCRF. The investigator will report the eCRFs to the sponsor and retain a copy of the eCRFs.

## 11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents.

## 11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

## 11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

## 11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

## 11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

## 11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or CTA executed between the institution/investigator and the sponsor/CRO.

## 11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

## 11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

# 12 APPENDICES

## Appendix 1 Sponsor's Grading for Laboratory Values

(revised per Amendment 01)

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **BLOOD/BONE MARROW** | | | | |
| Hemoglobin (conversion from g/dL×0.6206) | **Female** (ULN=15.9 g/dL)<br><11.1 – 10.0 g/dL<br><111 – 100 g/L<br><6.9 – 6.2 mmol/L<br>**Male** (ULN=17.7 g/dL)<br><12.6 – 10.0 g/dL<br><126 – 100 g/L<br><7.8 – 6.2 mmol/L | <10.0 – 8.0 g/dL<br><100 – 80 g/L<br><6.2 – 4.9 mmol/L | <8.0 g/dL<br><80 g/L<br><4.9 mmol/L;<br>transfusion indicated | life-threatening consequences; urgent intervention indicated |
| Leukocytes (total white blood cell) | <3.40 – 3.0×$10^9$/L<br><3.40 $10^3$/uL – 3000/$mm^3$<br>(ULN=10.80 $10^3$/μL) | <3.0 – 2.0×$10^9$/L<br><3000 – 2000/$mm^3$ | <2.0 – 1.0×$10^9$/L<br><2000 – 1000/$mm^3$ | <1.0×$10^9$/L<br><1000/$mm^3$ |
| Lymphocytes | not applicable | <700 – 500/$mm^3$<br><0.7 – 0.5×$10^9$/L | <500 – 200/$mm^3$<br><0.5 – 0.2×$10^9$/L | <200/$mm^3$<br><0.2×$10^9$/L |
| Neutrophils | not applicable | <1.4 – 1.0×$10^9$/L<br><1400 – 1000/$mm^3$ | <1.0 – 0.5×$10^9$/L<br><1000 – 500/$mm^3$ | <0.5×$10^9$/L<br><500/$mm^3$ |
| Platelets | <155 – 75.0×$10^9$/L<br><155 $10^3$/uL – 75,000/$mm^3$<br>(ULN=379 $10^3$/μL) | <75.0 – 50.0×$10^9$/L<br><75,000 – 50,000/$mm^3$ | <50.0 – 25.0×$10^9$/L<br><50,000 – 25,000/$mm^3$ | <25.0×$10^9$/L<br><25,000/$mm^3$ |
| **METABOLIC/LABORATORY** | | | | |
| Albumin, serum- low (hypoalbuminemia) | **2 - 59 years** (ULN=5.5 g/dL)<br><3.5 – 3 g/dL<br><35 – 30 g/L<br>**59 -69 years** (LLN-ULN)<br><3.6 g/dL – 3 g/dL<br>**69 -79 years** (LLN-ULN)<br><3.5 g/dL – 3g/dL<br>**79 -89 years** (LLN-ULN)<br><3.5g/dL – 3g/dL | <3 – 2 g/dL<br><30 – 20 g/L | <2 g/dL<br><20 g/L | life-threatening consequences; urgent intervention indicated |
| Alkaline phosphatase | **Female:**<br>**18 -19 years**<br>>101 – 3.0×101<br>**19 -61 years**<br>ULN=107<br>**61 -71 years**<br>ULN=112<br>**71 -150 years**<br>ULN=108<br>**Male**<br>**18 -19 years**<br>>127 – 3.0×127<br>**19 -61 years**<br>ULN=102<br>**61 -71 years**<br>ULN=103<br>**71 -150 years**<br>ULN=105 | >3.0 – 5.0×ULN<br>See previous column for ULN values | >5.0 – 20.0×ULN<br>See previous column for ULN values | >20.0×ULN<br>See previous column for ULN values |
| Alanine aminotransferase | **Female:**<br>>32 – 3.0×32 | **Female:**<br>>3.0 – 5.0×32 | **Female:**<br>>5.0 – 20.0×32 | **Female:**<br>>20.0×32 |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| | **Male:**<br>>44 – 3.0 x 44 | **Male**<br>>3.0 – 5.0×44 | **Male:**<br>>5.0 – 20.0×44 | **Male:**<br>>20.0×44 |
| Aspartate aminotransferase | >40 – 3.0×40 | >3.0 – 5.0×40 | >5.0 – 20.0×40 | >20.0×40 |
| Bilirubin (hyperbilirubinemia) | >1.2 – 1.5×1.2 | >1.5 – 3.0×1.2 | >3.0 – 10.0×1.2 | >10.0×1.2 |
| Calcium, serum-low (hypocalcemia) (conversion to mmol×0.25) | <8.5 – 8.0 mg/dL<br><2.13 – 2.0 mmol/L | <8.0 – 7.0 mg/dL<br><2.0 – 1.75 mmol/L | <7.0 – 6.0 mg/dL<br><1.75 – 1.5 mmol/L | <6.0 mg/dL<br><1.5 mmol/L |
| Calcium, serum-high (hypercalcemia) | >10.6 – 11.5 mg/dL<br>>2.65 – 2.9 mmol/L | >11.5 – 12.5 mg/dL<br>>2.9 – 3.1 mmol/L | >12.5 – 13.5 mg/dL<br>>3.1 – 3.4 mmol/L | >13.5 mg/dL<br>>3.4 mmol/L |
| Cholesterol, serum-high (hypercholesterolemia) (conversion to mmol/L ×0.02586) | **0 -19 years**<br>>169 – 300 mg/dL<br>>4.37 – 7.75 mmol/L<br>**19 -150 years**<br>>199 – 300 mg/dL<br>>5.15 – 7.75 mmol/L | >300 – 400 mg/dL<br>>7.75 – 10.34 mmol/L | >400 – 500 mg/dL<br>>10.34 – 12.92 mmol/L | >500 mg/dL<br>>12.92 mmol/L |
| Creatinine | **Female**<br>>1.00 mg/dL – 1.5×1.00<br>**Male**<br>>1.27 mg/dL – 1.5×1.27 | **Female**<br>>1.5 – 3.0×1.00<br>**Male**<br>>1.5 mg/dL – 3.0×1.27 | **Female**<br>>3.0 – 6.0×1.00<br>**Male**<br>>3.0 mg/dL – 6.0 ×1.27 | **Female**<br>>6.0×1.00<br>**Male**<br>>6.0×1.27 |
| Gamma glutamyl transpeptidase | **Female**<br>>60 IU/L – 3.0×60<br>**Male**<br>>65 IU/L – 3.0×65 | **Female**<br>>3.0 – 5.0×60<br>**Male**<br>>3.0 – 5.0×65 | **Female**<br>>5.0 – 20.0×60<br>**Male**<br>>5.0 – 20.0×65 | **Female**<br>>20.0×60<br>**Male**<br>>20.0×65 |
| Glucose, serum-high (hyperglycemia) (conversion to mmol/L ×0.0555) | **Fasting glucose value**<br>>99 – 160 mg/dL<br>>5.5 – 8.9 mmol/L | **Fasting glucose value**<br>>160 – 250 mg/dL<br>>8.9 – 13.9 mmol/L | >250 – 500 mg/dL;<br>>13.9 – 27.8 mmol/L;<br>hospitalization indicated | >500 mg/dL;<br>>27.8 mmol/L;<br>life-threatening consequences |
| Glucose, serum-low (hypoglycemia) | <65 – 55 mg/dL<br><3.6 – 3.0 mmol/L | <55 – 40 mg/dL<br><3.0 – 2.2 mmol/L | <40 – 30 mg/dL<br><2.2 – 1.7 mmol/L | <30 mg/dL<br><1.7 mmol/L<br>life-threatening consequences;<br>seizures |
| Phosphate, serum-low (hypophosphatemia) (conversion to mmol/L ×0.323) | not applicable | <2.5 – 2.0 mg/dL<br><0.8 – 0.6 mmol/L | <2.0 – 1.0 mg/dL<br><0.6 – 0.3 mmol/L | <1.0 mg/dL<br><0.3 mmol/L<br>life-threatening consequences |
| Potassium, serum-high (hyperkalemia) | not applicable | >5.5 – 6.0 mmol/L | >6.0 – 7.0 mmol/L<br>hospitalization indicated | >7.0 mmol/L<br>life-threatening consequences |
| Potassium, serum-low (hypokalemia) | <3.5 mEq/L – 3.0 mmol/L | <LLN – 3.0 mmol/L;<br>symptomatic; intervention indicated | <3.0 – 2.5 mmol/L<br>hospitalization indicated | <2.5 mmol/L<br>life-threatening consequences |
| Sodium, serum-high (hypernatremia) | >144 mEq/L – 150 mmol/L | >150 – 155 mmol/L | >155 – 160 mmol/L<br>hospitalization indicated | >160 mmol/L<br>life-threatening consequences |
| Sodium, serum-low (hyponatremia) | <134 mEq/L – 130 mmol/L | Not applicable | <130 – 120 mmol/L | <120 mmol/L<br>life-threatening consequences |
| Triglyceride, serum-high (hypertriglyceridemia) | 150 – 300 mg/dL<br>1.71 – 3.42 mmol/L | >300 – 500 mg/dL<br>>3.42 – 5.7 mmol/L | >500 – 1000 mg/dL<br>>5.7 – 11.4 mmol/L | >1000 mg/dL<br>>11.4 mmol/L<br>life-threatening consequences |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Uric acid, serum-high (hyperuricemia) | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | Not applicable | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | >10 mg/dL<br>>0.59 mmol/L<br>life-threatening consequences |

LLN = lower limit of normal, ULN = upper limit of normal.

# Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1 through Listing 5. Medications permitted with restrictions are listed in Listing 6 through Listing 8. (revised per Amendment 04) **These may not be all-inclusive listings.** Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-202 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 8 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

## Prohibited Prior/Concomitant Medications

### Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Prohibited from 14 days (or 5 half-lives, whichever is longer) before Randomization until after the last treatment visit** | | |
| **Anti-arrhythmic/ abnormal heart rhythm** | | |
| Amiodarone | Cordarone; Pacerone | Incidence in females greater than males, Torsades de Pointes risk regarded as low |
| Disopyramide | Norpace | Incidence in females greater than males |
| Dofetillide | Tikosyn | |
| Ibutilide | Corvert | Incidence in females greater than males |
| Procainamide | Pronestyl; Procan | |
| Quinidine | Cardioquin; Quinaglute | Incidence in females greater than males |
| Sotalol | Betapace | Incidence in females greater than males |
| **Antihistamine/ allergic rhinitis** | | |
| Astemizole | Hismanal | No longer available in United States |
| Terfenadine | Seldane | No longer available in United States |
| **Anti-anginal/ heart pain** | | |
| Bepridil | Vascor | Incidence in females greater than males |
| **Antibiotic/ bacterial infection** | | |
| Clarithromycin | Biaxin | |
| Moxifloxacin | Avelox | |
| Sparfloxadin | Zagam | |
| **Listing 1 continued** | | |
| **Antimalarial/ malaria infection** | | |
| Chloroquine | Aralen | |
| Halofantrine | Halfan | Incidence in females greater than males |
| **Antipsychotic/ anti-emetic/ schizophrenia/ nausea** | | |
| Chloropromazine | Thorazine | |
| **Gastrointestinal stimulant/ heartburn** | | |
| Cisapride | Propulsid | |

## Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Antinausea/ nausea** | | |
| Domperidone | Motillum | Not available in the United States |
| **Sedative; antinausea/ anesthesia adjunct, nausea** | | |
| Droperidol | Inapsine | |
| **Antibiotic; gastrointestinal stimulant/ bacterial infection; increase gastrointestinal motility** | | |
| Erythromycin | Erythrocin; E.E.S. | Incidence in females greater than males |
| **Antipsychotic/ schizophrenia** | | |
| Haloperidol | Haldol | When given intravenously or at higher than recommended doses, risk of sudden death, QT prolongation, and torsades increases |
| Mesoridazine | Serentil | |
| Thioridazine | Mellaril | |
| **Opiate agonist/ pain control, narcotic dependence** | | |
| Levomethadyl | Orlaam | |
| Methadone | Methadose; Dolophine | Incidence in females greater than males |
| **Anti-infective/ pneumocystis pneumonia** | | |
| Pentamidine | Pentam; NebuPent | Incidence in females greater than males |
| **Antipsychotic/ Tourette's tics** | | |
| Pimozide | Orap | Incidence in females greater than males |
| **Antilipemic/ hypercholesterolemia** | | |
| Probucol | Lorelco | No longer available in United States |
| **Anticancer** | | |
| Arsenic trioxide | Trisenox | Used for leukemia |
| Vandetanib | Zactima | Used for thyroid cancer |

Note: This list is not exhaustive.

QTc = Corrected QT interval.

## Listing 2 Prohibited Medications Within 5 Half-lives or 60 days, Whichever is Longer, Before Randomization and Until after the Last Treatment Visit

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Systemic Immunosuppressants[a,b] and Immunomodulatory therapy** | |
| Azathioprine | Azasan, Imur |
| Ciclosporine | Gengraf, Neoral |
| Dexamethasone | Decadron, Dexasone, Diodex, Hexadrol, Maxidex |
| Fingolimod | Gilenya |
| Methotrexate | Trexall |
| Methylprednisolone | Medrol, Meprolone |
| Mycophenolate | CellCept, Myfortic |
| Prednisolone | Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS |

Note: This list is not exhaustive.

a: Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

b: During the treatment period of the study, short term (not more than 14 days) use of steroids up to the equivalent of prednisolone 40 mg OD is permitted after discussion with the Medical Monitor. Dosing with study drug should be suspended from the time steroid treatment is started. Complete blood count and lymphocyte subsets should be determined prior to starting steroid treatment and continue to be monitored weekly. Study drug may be resumed after discussion with the Medical Monitor when the following conditions are met: (1) treatment with steroids has been completed for at least 1 week; (2) absolute lymphocytes not <LLN; (3) no lymphocyte subsets are below the discontinuation threshold (for Core Study only); (4) the investigator considers that the medical condition which required treatment with steroids has improved or resolved. Weekly testing of lymphocyte subset counts (for Core Study only) and CBC with differentials is required for 4 weeks following resumption of study drug administration. (revised per Amendment 04)

## Listing 3 Prohibited Medications Within 6 Months Before Randomization

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Immunoglobulin therapy** | |
| Adalimumab | Humira |
| Bevacizumab | Avastin |
| Efalizumab | Raptiva |
| Etanercept | Enbrel |
| Immune globulin IV, IVIG, IGIV | Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S |
| Infliximab | Remicade |
| Omalizumab | Xolair |
| Ranibizumab | Lucentis |
| Other monoclonal antibodies not listed here | |

Note: This list is not exhaustive.

## Listing 4 Prohibited Live Vaccines Within 3 Months Before Randomization Until after the Last Treatment Visit (this does not apply to non-live/inactivated vaccines)

| **Bacterial vaccines** | **Viral vaccines** |
|---|---|
| Bacillus Calmette-Guérin vaccine against tuberculosis | Measles vaccination |
| Cholera vaccination (oral) | Rubella vaccination |
| | Oral polio vaccination (Sabin) |
| | Yellow fever vaccination |
| | Varicella (chickenpox) vaccination |
| | Rotavirus vaccination |
| | Japanese encephalitis vaccination |
| | Live attenuated influenza vaccine (FluMist, Fluenz) |
| Typhoid vaccination (oral) | Mumps vaccination |

Note: This list is not exhaustive

## Listing 5 Strong CYP3A4 Inhibitors Prohibited Within 5 Half-Lives or 14 Days (Whichever Is Longer) Before Randomization Until After the Last Treatment Visit

| Generic name | Brand name(s) |
|---|---|
| boceprevir | Victrelis |
| clarithromycin | Clarithromycin, clarithromycin extended release, Prevpac |
| cobicistat | Tybost, Stribild, |
| conivaptan | Vaprisol |
| danoprevir | |
| elvitegravir | Vitekta, Stribild |
| indinavir | Crixivan |
| itraconazole | Sporanoz, Onmel |
| ketoconazole | Xolegel, Nizoral, Ketodan |
| lopinavir | Kaletra |
| nefazodone | Serzone |
| nelfinavir | Viracept |
| posaconazole | Noxafil |
| ritonavir | Norvir, Kaletra |
| saquinavir | Invirase, Fortovase |
| telaprevir | Incivek |
| telithromycin | Ketek |
| tipranavir | Aptivus |
| troleandomycin | Triocetin |
| voriconazole | Vfend, Voriconazole |

Note: This list is not exhaustive

## Permitted Prior/Concomitant Medications

### Listing 6 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Baseline Cognitive Assessments at Visit 2 and Remain on the Same Stable Dose from Baseline to Final Follow-Up Visit

| **Generic name** | **Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™)** |
|---|---|
| **Cognitive Enhancers** | |
| Donepezil | Aricept |
| Galantamine | Reminyl |
| Memantine | Namenda |
| Rivastigmine | Exelon |

Note: This list is not exhaustive.

## Listing 7 Permitted Medications Used on PRN Basis Which are Not to be Used Within 72 Hours before Cognitive Testing

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Opiates** | |
| Morphine | Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol |
| **Opiate Agonists** | |
| Codeine | Codeine |
| Fentanyl | Actiq, Duragesic, Fentora, Onsolis, Sublimaze |
| Meperidine | Demerol, Meperitab |
| Oxycodone | Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol |
| Other opioids or opioid agonists which are used on PRN basis | |
| **Benzodiazepines and sedatives** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Amitriptyline | (various) |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Dothiepin | (various) |
| Estazolam | ProSom |
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |
| Lorazepam | Ativan |
| Midazolam | Versed |
| Olanzapine | Zyprexa |
| Promethazine | Phenergan; others |
| Ramelteon | Rozerem |
| Risperidone | Risperdal |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zolpidem | Ambien; others |
| Zopiclone | (various) |
| Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives | |

Note: This list is not exhaustive

## Listing 7 Permitted Medications Used on PRN Basis Which are Not to be Used Within 72 Hours before Cognitive Testing

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|

PRN = Pro re nata

## Listing 8 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| If to be used on a PRN basis see Listing 7. If to be used chronically, subjects must be on a stable dose for ≥4 weeks before Baseline. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks. | |
| **Antidepressants** | |
| Amitriptyline hydrochloride | Elavil |
| Amoxapine | Amoxapine |
| Bupropion | Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin |
| Citalopram | Celexa |
| Clomipramine hydrochloride | Anafranil |
| Desipramine hydrochloride | Norpramin |
| Desvenlafaxine | Pristiq |
| Doxepin hydrochloride | Prudoxin, Silenor, Sinequan, Zonalon |
| Duloxetine | Cymbalta |
| Escitalopram | Lexapro |
| Fluoxetine | Prozac, Sarafem, Selfemra |
| Fluvoxamine | Luvox |
| Imipramine hydrochloride | Tofranil |
| Isocarboxazid | Marplan |
| Maprotiline hydrochloride | Ludiomil |
| Mirtazapine | Remeron Soltab |
| Nortriptyline hydrochloride | Aventyl, Pamelor |
| Paroxetine | Paxil, Pexeva |
| Phenelzine | Nardil |
| Protriptyline hydrochloride | Vivactil |
| Rasagiline | Azilect |
| Selegiline | EMSAM |
| Sertraline | Sertaraline, Zoloft |
| Tranylcypromine | Parnate |
| Trazodone hydrochloride | Desyrel, Oleptro |
| Trimipramine maleate | Surmontil |
| Venlafaxine hydrochloride | Effexor |

## Listing 8 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Mood Stabilizers (Listing 8 continued)** | |
| Carbamazepine | Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR |
| Lamotrigine | Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR |
| Valproic acid | Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate |
| **Antipsychotics** | |
| Acetophenazine | Tindal |
| Aripiprazole | Abilify |
| Asenapine | Saphris |
| Olanzapine | Zyprexa |
| Chlorpromazine | Thorazine |
| Haloperidol | Haloperidol, Haldol |
| Clozapine | Clozaril, Fazaclo |
| Fluphenazine | Prolixin |
| L-Methylfolate | Deplin, L-Methylfolate Calcium |
| Loxapine | Loxitane |
| Mesoridazine | Serentil |
| Perphenazine | Trilafon |
| Quetiapine | Seroquel |
| Risperidone | Risperdal |
| Thioridazine | Mellaril |
| Thiothixene | Navane |
| Trifluoperazine | Stelazine |
| **Benzodiazepines** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Estazolam | ProSom |

## Listing 8 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |
| Lorazepam | Ativan |
| Midazolam | Versed |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zopiclone | Imovane, Zimovane |
| Zopidem | Ambien, Ambien CR, Intermezzo, Stilnox, Stilnoct, Sublinox, Hypnogen, Zolsana |

Note: This list is not exhaustive.

PRN = Pro re nata

# Appendix 3 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

## Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

## Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In

this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

### Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

### Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed

scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

# Appendix 4 AEs Indicating Signals of Possible Drug Abuse Potential

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| 1 | **Euphoric mood** | Euphoric mood |
| | | Euphoria |
| | | Euphoric |
| | | Exaggerated well-being |
| | | Excitement excessive |
| | | Feeling high |
| | | Felt high |
| | | High |
| | | High feeling |
| | | Laughter |
| 2 | **Elevated mood** | Elevated mood |
| | | Mood elevated |
| | | Elation |
| 3 | **Feeling abnormal** | Feeling abnormal |
| | | Cotton wool in head |
| | | Feeling dazed |
| | | Feeling floating |
| | | Feeling strange |
| | | Feeling weightless |
| | | Felt like a zombie |
| | | Floating feeling |
| | | Foggy feeling in head |
| | | Funny episode |
| | | Fuzzy |
| | | Fuzzy head |
| | | Muzzy head |
| | | Spaced out |
| | | Unstable feeling |
| | | Weird feeling |
| | | Spacey |
| 4 | **Feeling drunk** | Feeling drunk |
| | | Drunkenness feeling of |
| | | Drunk-like effect |
| | | Intoxicated |
| | | Stoned |
| | | Drugged |
| 5 | **Feeling of relaxation** | Feeling of relaxation |
| | | Feeling relaxed |
| | | Relaxation |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Relaxed |
| | | Increased well-being |
| | | Excessive happiness |
| **6** | **Thinking abnormal** | Thinking abnormal |
| | | Abnormal thinking |
| | | Thinking irrational |
| | | Thinking disturbance |
| | | Thought blocking |
| | | Wandering thoughts |
| **7** | **Hallucination** | Hallucination |
| | | Illusions |
| | | Flashbacks |
| | | Floating |
| | | Rush |
| | | Feeling addicted |
| **8** | **Inappropriate affect** | Elation inappropriate |
| | | Exhilaration inappropriate |
| | | Feeling happy inappropriately |
| | | Inappropriate affect |
| | | Inappropriate elation |
| | | Inappropriate laughter |
| | | Inappropriate mood elevation |
| **9** | **Mood disorders and disturbances** | Mental disturbance |
| | | Depersonalisation |
| | | Psychomotor stimulation |
| | | Mood disorders |
| | | Emotional and mood disturbances |
| | | Delirium |
| | | Delirious |
| | | Mood altered |
| | | Mood alterations |
| | | Mood instability |
| | | Mood swings |
| | | Emotional lability |
| | | Emotional disorder |
| | | Emotional distress |
| | | Personality disorder |
| | | Impatience |
| | | Abnormal behavior |
| | | Delusional disorder |
| | | Irritability |
| **10** | **Drug tolerance** | Drug tolerance |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Habituation |
| | | Drug withdrawal syndrome |
| | | Substance-related disorders |
| **11** | **Psychosis** | Psychosis |
| | | Psychotic episode or disorder |
| **12** | **Dissociative State** | Dissociation |
| | | Disconnected |
| | | Derealisation |
| | | Depersonalisation |
| | | Detached |
| | | Sensation of distance from one's environment |
| | | Loss of a sense of personal identity |

# Appendix 5 Eisai Lymphocyte Subset Criteria for Study E2609-G000-202: Justification for a Population-Adjusted Approach

**Introduction:**

The Eisai clinical study, E2609-G000-202, requires the analysis of absolute numbers of various functional subsets of circulating lymphocytes. These are distinguished by identification of various complementary differentiation (CD) markers on the cell surface using fluorescent-labeled antibody reagents and flow cytometry. Current enumeration of certain lymphocyte subsets form part of the immunologically based eligibility criteria for study enrollment, as well as being monitored for safety for enrolled and treatment randomized subjects. The Trucount™ M (Becton, Dickinson and Company [BD], BD Biosciences, San Jose, CA) antibody reagents used for the lymphocyte subset eligibility criteria, provides readouts for both absolute (BD Trucount tubes) and percentage of lymphocyte subsets, and includes the following CD markers: CD3 (T cells), CD4 (T helper cells), CD8 (cytotoxic T cells), CD16/56 (natural killer cells), CD14 (macrophages), and CD19 (B cells).

Trucount lymphocyte subset reference ranges provided by the reagent manufacturer (BD) for both absolute and percentages were established for clinical use as an in vitro diagnostic using standardized reference interval methodology. These LLN for the various lymphocyte subsets are currently being used by the central laboratory for Eisai Study E2609-G000-202 to determine eligibility of screened subjects and as part of safety assessments during post-randomization visits. The eligibility criterion excludes subjects with absolute counts of T and B cell markers (CD4, CD8, and CD19 respectively) less than the reference range lower limit of normal (<LLN) at Screening or Baseline.

**Need to assign age appropriate reference ranges:**

Reference ranges established by the vendor according to working group guidance[3] may not be representative of different subgroup analyses (eg, ancestry, disease state, age, gender, etc.), and therefore interval adjustment may be required depending on the subpopulation of interest. The working group guidance for reference intervals (CLSI, 2010[4]) recommends examining data to determine if >10% of subjects are outliers (ie, more than 10% < LLN), and if so, to initiate development of subgroup-appropriate intervals by analyzing data from the literature or internal studies representing the reference population [a minimum of 120 observations recommended by the guidance.[3]]

Data from the ongoing Study E2609-G000-202 has been examined and greater than 10% of the study population screening samples fall below the manufacturer recommended LLN for the key lymphocyte subsets. The population for Study E2609-G000-202 are patients aged 50 to 85 years old inclusive with Mild Cognitive Impairment due to AD or with Mild to Moderate dementia due to AD. Lymphocyte subset data from a data cut of 93 screened

subjects was analyzed and showed that both CD8 and CD4 had greater than 10% of the subjects with results <LLN (26.9%, <220 cells/mm$^3$ and 13%, <404 cells/mm$^3$, respectively); CD19 had approximately 10% of the subjects with results <LLN (9.7%, <80 cells/mm$^3$).

To further determine if the outlier data observations from the ongoing Study E2609-G000-202 were associated with disease status or age, lymphocyte subset data from additional Eisai studies that included healthy elderly subjects or patients diagnosed with MCI or mild/moderate AD were examined. The individuals from all 3 studies included the same 50-to 85-year-old age range as the current E2609-G000-202 study. The studies evaluated include: (1) Study E2609-A001-002 treatment study (n=50 healthy elderly); (2) Lymphocyte subset pilot study in healthy elderly [n=30]; and (3) Lymphocyte subset pilot study in AD/MCI [n=31]. Screening or baseline sample from all 4 studies had >10% of the CD8 absolute counts below reference LLN, 2 out of 4 had >10% of the CD19 absolute counts below reference LLN and 1 out of 4 had >10% of the CD4 absolute counts out of reference LLN [Table 10, Table 11, and Table 12]. The data suggests that the reference values of LLN for CD4, CD8, and CD19 subsets are not a disease-associated observation but are related to the age of the study population being evaluated.

In addition to the Eisai study data, age related decline in lymphocyte subsets has been described in the literature Yan et.al.[1][2] Analysis was performed using flow cytometry on peripheral blood leukocytes using healthy subjects across the 3rd and 10th decades of life. The results from the Yan study (n=80; 37 males, 43 females) demonstrated that with advancing age there was a significant decline in the percentage of lymphocytes, specifically naive T cells [CD3 *P*=0.03], cytotoxic T cells [CD8 *P*=0.08] and activated B cells [CD20/CD69 *P*=0.03] with certain subsets demonstrating even greater decline in males.[1] The age associated changes in immune capabilities, termed “immunosenescence”, which include degenerative changes in the lymph nodes, effects on lymphocyte subsets and changes in adaptive immunity may underlie the increased risk of infection and cancer and decreased immune function in the elderly. This, along with the data from the four Eisai studies described earlier, support the readjustment of the LLNs for the CD reference ranges used for eligibility in Study E2609-G000-202 such that they are better suited to the older patient population enrolling in this study which is thought to be representative of the wider patient population.

**Determining the new LLN criteria:**

The recommended method for establishing reference intervals is the nonparametric approach where the underlying distribution of the data does not matter. The values received from the data (a minimum of 120 observations representing the subgroup population of interest is recommended) are rank ordered and can be used to evaluate the comparative reference interval.[3]

When data from the 4 Eisai studies are put in rank order (see Table 10, Table 11, and Table 12), and a 10% cut value is applied to each of the 3 CD markers of interest the following age-adjusted LLN values are generated:

**Table 9 Summary of CD4, CD8, and CD19 LLNs and Age-Adjusted LLNs**

| Lymphocyte Subset | Current LLN | Age-adjusted LLN |
|---|---|---|
| CD4 absolute count | 404 cells/$mm^3$ | 396 cells/$mm^3$ |
| CD8 absolute count | 220 cells/$mm^3$ | 157 cells/$mm^3$ |
| CD19 absolute count | 80 cells/$mm^3$ | 74 cells/$mm^3$ |

**Table 10 Summary of CD Counts (Parameter: CD19)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 30 | 203 |
| Mean | 213.47 | 198.49 | 159.20 | 172.77 | 192.57 |
| Median | 189.66 | 163.00 | 118.50 | 159.50 | 164.86 |
| 5th percentile | 84.81 | 59.00 | 38.00 | 69.00 | 59.00 |
| 10th percentile | 102.26 | 81.00 | 42.00 | 70.50 | 74.00 |
| 25th percentile | 139.66 | 104.00 | 75.00 | 100.00 | 104.58 |
| 75th percentile | 261.51 | 225.00 | 225.00 | 246.00 | 246.00 |
| 95th percentile | 376.67 | 443.00 | 424.00 | 384.00 | 402.00 |
| Range | 66.19, 593.48 | 17.00, 1066.00 | 37.00, 455.00 | 39.00, 415.00 | 17.00, 1066.00 |

**Table 11 Summary of CD Counts (Parameter: CD8)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 31 | 204 |
| Mean | 362.72 | 352.18 | 324.63 | 427.74 | 362.20 |
| Median | 364.74 | 330.00 | 344.00 | 315.00 | 336.39 |
| 5th percentile | 115.02 | 138.00 | 86.00 | 100.00 | 115.02 |
| 10th percentile | 170.24 | 151.00 | 159.50 | 153.00 | 157.00 |
| 25th percentile | 253.37 | 213.00 | 204.00 | 217.00 | 230.00 |
| 75th percentile | 465.52 | 425.00 | 405.00 | 494.00 | 438.00 |
| 95th percentile | 614.57 | 716.00 | 557.00 | 988.00 | 702.00 |
| Range | 98.45, 702.50 | 37.00, 803.00 | 61.00, 702.00 | 54.00, 2255.00 | 37.00, 2255.00 |

**Table 12 Summary of CD Counts (Parameter: CD4)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 31 | 204 |
| Mean | 846.15 | 839.58 | 789.27 | 804.52 | 828.46 |
| Median | 836.94 | 805.00 | 777.50 | 771.00 | 791.50 |
| 5th percentile | 388.44 | 337.00 | 395.00 | 351.00 | 344.00 |
| 10th percentile | 479.55 | 361.00 | 490.00 | 427.00 | 396.00 |
| 25th percentile | 639.54 | 620.00 | 661.00 | 669.00 | 633.77 |
| 75th percentile | 1031.49 | 1078.00 | 924.00 | 1014.00 | 1039.50 |
| 95th percentile | 1315.55 | 1404.00 | 1124.00 | 1327.00 | 1347.00 |
| Range | 274.90, 1643.55 | 197.00, 1481.00 | 248.00, 1720.00 | 143.00, 1336.00 | 143.00, 1720.00 |

References:

1. Yan et al., Immunity and Ageing 2010 v. 7:4; The effect of ageing on human lymphocyte subsets: comparison of males and females.
2. Wikby et al., Biogerontology 2008 vol 9: 299; The immune risk profile is associated with age and gender: findings from three Swedish population studies of individuals 20-100 years of age.
3. Horowitz eJIFCC 2008 vol. 19 (2) Reference intervals: practical aspects).
4. Horowitz et al., CLSI Vol 28 no. 30 Clinical and Laboratory Standards Institute's (CLSI) newly revised document Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition (C28-A3), published in November 2010 EP28-AC3

## Appendix 6 Open-Label Extension Phase

(revised per Amendment 07)

### PRIMARY OBJECTIVE

- To assess the long-term safety and tolerability of daily dosing with elenbecestat (E2609) 50 mg in mild cognitive impairment (MCI)/Prodromal subjects and in subjects with Mild to Moderate Dementia due to Alzheimer's Disease

### SECONDARY OBJECTIVES

- To explore the long-term effects of elenbecestat (E2609) on clinical status by assessment of:
    a. The Mini-Mental State Examination (MMSE)
    b. The Functional Assessment Questionnaire (FAQ; also known as the Functional Activities Questionnaire)
- To explore the long-term effects of elenbecestat (E2609) on:
    a. vMRI including total hippocampal volume, left and right hippocampal volume, whole brain volume, and total ventricular volume with up to 24 months of treatment in the OLE Phase.
    b. Plasma amyloid at 12 and 24 months of treatment in the OLE Phase

### ELIGIBILITY CRITERIA

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

Inclusion:

1. Subjects who complete the 18-month treatment and the 12-week follow-up period (Visit 20) in the Core Study and whose Visit 20 falls within a 4-week window from the start of the Open-label Extension (OLE) Phase (Visit 21). Permission must be obtained from the Medical Monitor if Visit 21 is to occur more than 4 weeks from Visit 20.
2. Subjects must continue to have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the OLE Phase.

Exclusion:

1. Subjects who discontinue study drug prematurely during the Core Study are not eligible to participate in the OLE Phase.

2. Subjects with any active infection within 4 weeks of Visit 21.
3. Subjects with absolute lymphocyte count below the Lower Limit of Normal (LLN) within 10 days of Visit 21.
4. Subjects who develop the following conditions from the time of screening for the Core Study to the start of the OLE Phase:
    a. Hepatic impairment, with total bilirubin greater than 1.5 × upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7. Subjects with Gilbert's syndrome need not be excluded on the basis of an elevated bilirubin, provided that they have no other signs or symptoms suggestive of hepatic impairment.
    b. Any contraindications to MRI scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners).
    c. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately.
    d. Immunoglobulin (Ig) deficiency or other immunodeficiency disorders
    e. Chronic viral hepatitis.
    f. Tuberculosis (TB).
    g. Ophthalmic shingles.
    h. Ocular herpes simplex virus (HSV) infection.
    i. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
        - Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
        - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
        - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
    j. Malignant neoplasms (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject from OLE).
5. Subjects with prolonged QTcF interval at Visit 20 or Visit 21. Subjects with a single 12-lead ECG QTcF >450 msec should have 2 additional ECGs performed at least 1 min

apart and the mean QTcF from the triplicate ECGs should be calculated. Subjects with a mean QTcF value >450 msec are not eligible to enter the OLE Phase.

6. Subjects with significant pathological findings on brain MRI including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).
7. Subjects who have a "yes" answer to the Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation questions 4 or 5 at Visit 20 or Visit 21 or any suicidal behavior during the study prior to the start of the OLE Phase.
8. Female subjects of child bearing potential who meet any of the follow criteria:
    a. Do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period and for 28 days after study drug discontinuation.
    b. Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.
    c. Who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
9. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Visit 20 or Visit 21.
10. Subjects with medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments.
11. Any other clinically significant abnormal findings in vital signs, ECGs and laboratory tests that would, in the investigator's opinion, would affect the subject's safety or interfere with study assessments during the OLE Phase.

## STUDY DESIGN AND PLAN

The OLE Phase allows eligible subjects to receive elenbecestat (E2609) 50 mg for up to 24 months (2 years).

Subjects who are enrolled in the Core Study will have the option to participate in the OLE Phase provided that they complete the Core Study (which include 18 months of double-blind treatment and 12 weeks of Follow-up Period) and satisfy the entry criteria for the OLE Phase. Subjects who discontinue from study drug during the Core Study are not eligible to participate in the OLE Phase.

Eligible subjects who choose to participate in the OLE Phase may enter the OLE Phase immediately following the completion of Visit 20 (ie, Visit 21 procedures may be completed on the same day as Visit 20). Subjects who are eligible to participate in the OLE Phase but who do not transition to the OLE Phase on the day of Visit 20 may enter the OLE Phase any time within 4 weeks of Visit 20. The Medical Monitor must be contacted if Visit 21 is to occur more than 4 weeks after Visit 20. For all subjects, assessments performed at V20 may serve as baseline values for the OLE Phase (ie, results of assessments conducted at Visit 21) with exceptions of laboratory assessments and vital signs, which must be repeated if Visit 21 occurs more than 10 days from Visit 20.

During the OLE Phase, subjects will receive open-label elenbecestat (E2609) 50 mg per day for up to 24 months. Subjects with pending INR and serum pregnancy test results (females subjects of child bearing potential only) but who are otherwise qualified may begin OLE dosing at Visit 21; however, these subjects must discontinue study drug treatment immediately if either test result meet the exclusion criteria.

Safety assessments will be performed as described in Table 14. Subjects may discontinue from study drug for any reason. Subjects who complete 24 months of OLE treatment or who discontinue the study drug must comply with the Early Discontinuation Visit (within 7 days after the last dose of study drug) and the Follow-Up Visits (weeks 4 and 12 after the last dose of study drug).

The study will end when the last visit for the last subject has completed the OLE Phase.

**Removal of Subjects from Therapy or Assessment**

The investigator may discontinue study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to stop study drug or withdraw from the study at any time for any reason. Subjects who discontinue study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. Subjects who discontinue from treatment during the OLE will have 2 posttreatment Follow-Up visits at 4 and 12 weeks after the last dose of study drug.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug should be collected on the ED from study drug electronic case report form (eCRF) page (see Protocol Section 9.5.5). In addition, the date of last dose of study drug will be recorded on the Study Drug Dosing eCRF page.

Safety-related criteria for discontinuation of study drug include the following:

1. Absolute lymphocyte count will be monitored during the study. Should a subject develop lymphocytopenia (less than 800/mm$^3$ or LLN, whichever is higher), a confirmation test should occur as soon as possible but no later than within 5 days with a repeat test of absolute lymphocytes. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm$^3$) should be handled as above. If a 2nd occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm$^3$), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug.

2. A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), will be discontinued from study drug and a dermatologic consult will be requested regardless of whether the rash is considered drug-related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

3. Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

4. Development of any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. If discontinued from study drug, subjects will undergo an ED Visit within 7 days after discontinuation. They will also undertake an Unscheduled Visit (with MRI) at approximately 4 weeks after the visit at which such MRI features were first identified. Additional visits for safety may be arranged if clinically indicated in the opinion of the investigator, including after 12 weeks after the last dose of study drug. At any time during the treatment period, subjects who have asymptomatic, treatment-emergent microhemorrhages as detected by MRI, but none of the features which merit

discontinuation of treatment (ie, vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic treatment-emergent microhemorrhage) may continue with treatment. These subjects will have safety assessments (including MRI) at approximately 4 weeks after the visit at which such MRI features were found. They will also continue with the scheduled MRI scans. Additional unscheduled MRI scans may be arranged on an individual subject basis in discussion with the study medical monitor.

5. Pregnancy
6. A postdose ECG with an average QTcF interval >500 msec from triplicate ECGs.
7. A postdose ECG with a QTcF interval increase from baseline >60 msec and a QTcF interval >450 msec as demonstrated from triplicate ECGs.

**Treatments**

During the OLE Phase, all subjects will receive open-label elenbecestat (E2609) 50 mg once a day. Each subject will take 1 tablet orally QD, with food. Please refer to Table 14 for specific information on drug administration on days when PD sampling is to be performed.

**EXTENSION PHASE ASSESSMENTS**

Safety assessments will continue to be monitored according to the Schedule of Assessments and all adverse events (AEs) and serious adverse events (SAEs) recorded. All safety assessments (eg, physical examinations, neurological examinations, vital signs, hematology, blood chemistry, serum and urine pregnancy test for females of child bearing potential, safety MRI and vMRI) will be performed as described in Table 14. The number of blood samples and the total volume of blood that will be collected throughout OLE Phase is summarized in Table 13.

There will be no centralized dermatological assessments in the OLE Phase; however, dermatological assessments will be performed by the investigator at every scheduled visit and as needed, at an unscheduled visit. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly.

Full neurologic examinations will be performed at the start of the OLE (Visit 20 or 21), and every 6 months during the OLE treatment period. An additional neurologic examination will also be performed at the final Follow-Up Visit. The neurologic examinations will include

muscle strength testing and assessment of cranial nerves including olfaction, with the use of the Brief Smell Identification Test, as well as other parts of the central nervous system (CNS).

Complete blood counts and percentages will be measured (by a centralized laboratory) every scheduled visit. Additional blood sample will be collected and stored at each scheduled visit; these samples may be used for exploratory biomarker analyses or be analyzed in the event that the subject develops treatment-emergent adverse events that warrant further investigation.

Peripheral blood mononuclear cells (PBMCs) will be collected every scheduled visit and posttreatment for exploratory immunomodulatory and immune-based analyses. These blood samples will be collected at every visit and stored in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

Safety brain MRI and vMRI assessments will be performed at the end of the OLE treatment period (Visit 32 or ED). Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Assessment of suicidal ideation and behavior using the C-SSRS will be performed at the beginning and at the end of treatment and a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits.

Blood sample for PD analyses will be collected at Week 53 (Visit 28), at the end of the OLE treatment period (Visit 32 or ED), and during the Follow-up Period (Visits 33 and 34). The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. The blood sample for PD analyses should be collected at fasting or at least 2 hours after the most recent meal.

Clinical assessments (MMSE and FAQ) will be administered every 3 months as described in Table 14.

The Follow-Up Visit will take place at weeks 4 and 12 after the last dose of study drug as described in Table 14. These assessments will also be performed if a subject prematurely discontinues from the OLE Phase.

**Table 13 Summary of Blood Sample Volumes**

| Assessment | Total number of collection time points[a] | Number of time points x volume per collection (mL) | Total volume (mL) |
|---|---|---|---|
| | | OLE Treatment and Follow-up Periods | |
| **Blood** | | | |
| Clinical Chemistry | 14 | 14 x 2 mL | 28 mL |
| Hematology | 14 | 14 x 5 mL | 70 mL |
| Lymphocyte subset analyses[b] | 14 | 14 x 4 mL | 56 mL |
| PBMC | 14 | 14 x 16 mL | 224 mL |
| PT, PTT for INR | 1 | 1 x 3 mL | 3 mL |
| Serum Pregancy Test | 1 | 1 x 2 mL | 2 mL |
| Sample for immune status[c] | 8 | 8 x 4 mL | 32 mL |
| PD sample | 5 | 5 x 4 mL | 20 mL |
| Total volume whole blood collected | | | 435 mL |

OLE = Open-label Extension, PBMC = peripheral blood mononuclear cell, PT = prothrombin time, PTT = partial thromboplastin time, INR = International Normalized Ratio, PD = pharmacodynamics.

a: Total collection time points include a baseline sample at Visit 21 if not done at Visit 20; a baseline sample will be collected only if Visit 21 is conducted more than 10 days after Visit 20.

b: Blood samples for lymphocyte subset analyses will be collected and analyzed at every visit; reports of the analyses will be sent to the Sponsor only.

c: Blood samples for will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

## STUDY DRUG SUPPLIES

Elenbecestat (E2609) tablets of 50-mg dose strengths will be supplied. Each subject will take 1 tablet per day.

## SCHEDULE OF PROCEDURES/ASSESSMENTS

Table 14 presents the Schedule of Procedures/Assessments for the OLE Phase.

## Table 14 Schedule of Procedures/Assessments in Study 202: Open-label Extension Phase

| **Phase** | **Open-label Extension Phase** | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | **Follow-Up[d]** | | **UNS Visit[e]** |
| **Visit[a]** | **21[b]** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **30** | **31** | **32** | **ED[c]** | **33** | **34** | |
| **Day in OLE** | **1** | **15** | **29** | **57** | **85** | **183** | **274** | **365** | **456** | **547** | **638** | **729** | | **757** | **813** | |
| **Week in OLE** | **1** | **3** | **5** | **9** | **13** | **27** | **40** | **53** | **66** | **79** | **92** | **105** | | **109** | **117** | |
| **Weeks elapsed since 1st dose in OLE** | **0** | **2** | **4** | **8** | **12** | **26** | **39** | **52** | **65** | **78** | **91** | **104** | | **108** | **116** | |
| **Nominal months elapsed since first dose in OLE** | **0** | | **1** | **2** | **3** | **6** | **9** | **12** | **15** | **18** | **21** | **24** | | **25** | **27** | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | |
| Routine physical examination with dermatologic review | X[f,g] | X | X | X | X | X | X | X | X | X | X | X | X | X | X[h] | X |
| Inclusion and Exclusion criteria | X | | | | | | | | | | | | | | | |
| Vital signs, including respiratory rate[i] | X[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | X[h] | X |
| Weight | X[f] | | | | | | | X | | | | X | X | | | X |
| Neurological examination[k] | X[f] | | | | | X | | X | | X | | X | X | | X | X |
| Concomitant medications[l] | X[m] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG[n] | X[f] | | | | X | X | | X | | X | | X | X | X | X[h] | X |
| Clinical biochemistry and urinalysis | X[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete blood count | X[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood sample for PT and PTT for INR | X | | | | | | | | | | | | | | | |
| Blood samples for lymphocyte subset analysis[o] | X[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood samples for PD and exploratory biomarkers[p] | X[f] | | | | | | | X | | | | X | X | X | X | X |
| Blood samples (isolation of PBMCs) | X[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Urine pregnancy test (females of CBP only)[q] | X | | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Serum pregnancy test (females of childbearing potential only) | X | | | | | | | | | | | | | | | X |
| Blood sample (storage for immune status)[r] | X[f] | | X | | X | X | | X | | | | X | X | X | X | X |
| MMSE[s] | X[f] | | | | X | X | X | X | X | X | X | X | X | X | X | X |
| FAQ[s] | X[f] | | | | X | X | X | X | X | X | X | X | X | X | X | X |

| Phase | Open-label Extension Phase | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Period | Treatment | | | | | | | | | | | | | Follow-Up[d] | | UNS Visit[e] |
| Visit[a] | 21[b] | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | ED[c] | 33 | 34 | |
| Day in OLE | 1 | 15 | 29 | 57 | 85 | 183 | 274 | 365 | 456 | 547 | 638 | 729 | | 757 | 813 | |
| Week in OLE | 1 | 3 | 5 | 9 | 13 | 27 | 40 | 53 | 66 | 79 | 92 | 105 | | 109 | 117 | |
| Weeks elapsed since 1st dose in OLE | 0 | 2 | 4 | 8 | 12 | 26 | 39 | 52 | 65 | 78 | 91 | 104 | | 108 | 116 | |
| Nominal months elapsed since first dose in OLE | 0 | | 1 | 2 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | | 25 | 27 | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | |
| C-SSRS | X[f] | | | | | | | | | | | X | X | | | |
| Clinical assessment of suicidal thinking and behavior[t] | | X | X | X | X | X | X | X | X | X | X | | | X | X | X |
| Safety MRI and vMRI[u] | X[f] | | | | | | | | | | | X | X | | | X |
| Adverse events | X[m] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dispense study drug | X[v] | | X | X | X | X | X | X | X | X | X | | | | | |

**Notes for Table 14**

C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, OLE = Open-label Extension, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, UNS = unscheduled, vMRI = volumetric magnetic resonance imaging.

a: A window of ±3 days will be permitted for Visits 22 and 23. A window of ±7 days will be permitted for Visits 24 and 25. A window of ±10 days will be permitted for Visit 26 to 32 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If a permitted visit windows is used, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose in OLE" at subsequent visits.

b: Visit 21 may occur on the same day or within 4 weeks of Visit 20 date. The Medical Monitor must be contacted if Visit 21 is to occur more than 4 weeks after Visit 20. Informed consent must be obtained prior to performing Visit 21 assessments.

c: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visits 33 and 34 respectively).

d: All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete the 2 posttreatment Follow-Up Visits; (ie, Visits 33 and 34). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-up Period.

e: Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

f: Result from Visit 20 will also serve as Visit 21 result. If the specified assessment was not performed at V20, it must be performed at Visit 21.

g: Dermatologic assessment by the investigator must be performed at Visit 21 in addition to the centralized skin assessment (using standardized photography) performed at Visit 20.

h: Only if clinically significant abnormalities are found at Visit 33 and the investigator considers it necessary to repeat at Visit 34.

i: Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

j: Result from Visit 20 will also serve as Visit 21 result if Visit 21 occurs within 10 days from Visit 20. If Visit 21 occurs more than 10 days after Visit 20, the assessment must be repeated at Visit 21.

k: Examples of neurological signs that may indicate new central nervous system pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. The Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits and serves as part of the neurologic examination.

l: Please refer to Section 9.4.7 which describes prohibited and permitted medications in the study.

m: Result from Visit 20 will also serve as Visit 21 result if Visit 21 occurs on the same day as Visit 20. If Visit 21 occurs more than 1 days after Visit 20, the assessment must be repeated at Visit 21.

n: Single 12-lead standard ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

o: Reports of the lymphocyte subset analyses will be sent to the Sponsor only. Lymphocyte subsets will include but are not limited to the following cell surface marker assessments: CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [NK cells] and CD14 [macrophages]) and absolute lymphocytes. Regulatory T cells will also be measured. Viability staining may also be employed.

p: PD blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day. All PD blood samples should be collected predose.

q: If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

r: Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

s: The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws).

t: The clinical assessment of suicidality will require input from both the subject and the study partner

u: MRI imaging will be conducted on separate days from the scheduled visits. Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images in MRI will be read by an approved central reader. MRI imaging should be conducted within 7 days before Visits 21 (where applicable) and 32. In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

v: The subject will take the first dose of study drug at the study site and the subject will be encouraged to stay at the site for an appropriate period of time as determined by the PI or Safety Physician for postdose medical observation. Subjects with pending INR and serum pregnancy results may begin dosing at Visit 21 if they satisfy all other OLE entry criteria.

## EXTENSION PHASE STATISTICAL METHODS

### Primary Endpoint

- Safety endpoints: AE, vital sign, ECG, physical examination, clinical laboratory test, any relevant test of cognitive function to evaluate decline, and MRI parameter (microhemorrhage, vasogenic edema, and other clinically significant abnormalities).

### Secondary Endpoint

Changes from Core Study and OLE baselines in

- MMSE and FAQ at each visit assessed in the OLE Phase
- Plasma amyloid measurements at 12 and 24 months of OLE treatment
- Total hippocampal volume, left and right hippocampal volume, whole brain volume, and total ventricular volume with up to 24 months of OLE treatment as measured by vMRI

## OLE PHASE ANALYSIS SETS

- The **OLE Safety Analysis Set (OLE-SAS)** is the group of subjects who receive at least 1 dose of study drug during the OLE Phase.
- The **OLE Full Analysis Set (OLE-FAS)** is the group of subjects who receive at least 1 dose of study drug during the OLE Phase and have at least 1 postdose efficacy assessment during the OLE Phase.
- The **OLE PD Analysis Set** is the group of subjects who have at least 1 posttreatment PD measurement in the OLE Phase.

### Safety Analyses

Safety analysis will be performed similarly to the Core Study. All safety analyses will be based on OLE Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and changes from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements, and cognitive decline assessment such as MMSE will be summarized by using descriptive statistics.

### Efficacy Analyses

The following secondary efficacy endpoints will be summarized by descriptive statistics and/or graphs, using OLE-FAS:

- Changes from Core Study and OLE baselines in MMSE and FAQ scores
- Changes from Core Study and OLE baselines in total hippocampal volume, left and right hippocampal volume, whole brain volume, and total ventricular volume at up to 24 months as measured by vMRI

The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

**Pharmacodynamic Analyses**

The OLE PD Analysis Set will be used for the summaries and analyses of PD biomarkers. The percentage change in plasma amyloid measurements from Core Study and OLE baselines to 12 and 24 months of OLE treatment will be analyzed and presented graphically.

**SAMPLE SIZE RATIONALE**

Subjects who complete the Core Study will have the option to participate in the OLE Phase. There is no sample size calculation for the OLE Phase.

# PROTOCOL SIGNATURE PAGE

(revised per Amendment 05)

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01 and 05) |
| **Investigational Product Name:** | Elenbecestat* (E2609)<br>* pINN (revised per Amendment 07) |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |

**SIGNATURES**

Authors:

PPD

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Neurology Business Group
Eisai Inc.

Date

PPD

PPD

Neurology Business Group
Eisai Ltd.

Date

PPD

Neurology Business Group Eisai Inc.

Date

# INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01 and 05) |
| **Investigational Product Name:** | Elenbecestat* (E2609)<br>* pINN (revised per Amendment 07) |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

| Investigator | Signature | Date |
|---|---|---|

# REVISION HISTORY

**Revisions to Version 7.0**

**New version/date: Version 8.0 / 02 Nov 2016 (per Amendment 06)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Subjects currently receiving 5 or 15 mg E2609 will be re-assigned to 50 mg E2609 for the remainder of the double-blind treatment period provided they will receive at least 12 weeks of double-blind treatment after the re-assignment, (ie, no dose reassignments past Visit 17). | As E2609 50 mg has been selected as the appropriate dose for Phase 3 development, subjects should not continue with doses that are not being advanced clinically. Additionally, the re-assignment of subjects in E2609 5 and 15 mg to E2609 50 mg will further the safety and tolerability data in subjects exposed to E2609 50 mg. | Synopsis<br>• Study Design<br>• Number of Subjects<br>• Sample Size Rationale<br>Section 7.1<br>Section 9.1<br>Section 9.1.2.1<br>Section 9.4.1<br>Section 9.4.4<br>Section 9.5.2 |
| Clarified that one of the exploratory endpoints will analyze change from baseline in CSF amyloid and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment only. There will no analysis for treatment follow-up. | Correction | Synopsis<br>• Analysis for Exploratory Endpoints<br>• Exploratory Objective<br>Section 8.3<br>Section 9.7.1.1.3<br>Section 9.7.1.6.3 |
| The frequency of DSMB safety reviews after the 12 week interim safety analysis will be reassessed and details will provided in the DSMB charter. | The DSMB charter will provide full details of interim safety reviews. | Synopsis<br>• Study Design<br>Section 9.1 |
| Removed the statement that subjects must be stable on AChEI or mementine to be included in the primary analyses. | This statement is no longer relevant as of Amendment 05. | Synopsis<br>• Concomitant Drug/Therapy<br>Section 9.4.7 |
| Added a statement to specify that additional analyses will be performed for subjects with dose re-assignment and details of these analyses and | To clarify that the SAP will be finalized prior to database lock and it will provide full details of the analyses to be performed for this study. | Section 9.7.1 |

**Revisions to Version 7.0**

**New version/date: Version 8.0 / 02 Nov 2016 (per Amendment 06)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| treatment group definitions will be provided in the statistical analysis plan (SAP); clarified that the SAP will be finalized before database lock. | | |
| Grammatical, typographical, and formatting changes | | Throughout |

**Revisions to Version 6.0**

**New version/date: Version 7.0 / 26 Sep 2016 (per Amendment 05)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Grammatical, typographical, and formatting changes | | Throughout |
| Removed Stage B from protocol. In line with this decision, the study objectives and endpoints have been modified and subjects who discontinue study drug early for any reason will no longer be required to complete efficacy visits after last dose of study drug. | This study will no longer be a Proof-of-Concept study. | Synopsis<br>• Study Protocol Title<br>• Investigators<br>• Sites<br>• Study Period and Phase of Development<br>• Objectives<br>• Study Design<br>• Early Discontinuation<br>• Number of Subjects<br>• Study Treatments<br>• Efficacy Assessments<br>• Safety Assessments<br>• Statistical Methods<br>• Study Endpoints<br>• Analysis Sets<br>• Efficacy and Biomarker Analyses<br>• Analysis for the Primary/Secondary/Exploratory Endpoints<br>• Pharmacokinetic Analyses<br>• Pharmacokinetic /Pharmacodynamic Analyses<br>• Interim Analyses<br>• Sample Size Rationale<br>Section 6<br>Section 7<br>Section 8<br>Section 8.3<br>Section 9.1<br>Section 9.2.1<br>Section 9.2.3<br>Section 9.2.4.4<br>Section 9.2.5<br>Section 9.3<br>Section 9.4.3 |

**Revisions to Version 6.0**

**New version/date: Version 7.0 / 26 Sep 2016 (per Amendment 05)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | | Section 9.4.4<br>Section 9.4.7<br>Section 9.2.5<br>Section 9.5.1.3.1<br>Section 9.5.1.4.2<br>Section 9.5.1.5.1<br>Section 9.5.2<br>Section 9.5.4.1<br>Section 9.5.5<br>Section 9.7<br>Section 10 |
| Updated Eisai contact information | Change in personnel and move to Building 100 | • Title Page<br>• Protocol Signature Page |

**Revisions to Version 5.0**

**New version/date: Version 6.0 / 29 Jun 2016 (per Amendment 04)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised number of investigational sites (from 40 to 35) | Feasibility | • Synopsis -<br>o Study Design<br>o Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Removed Exclusion Criterion No. 44 for male subjects regarding restrictions on child bearing | No longer a safety concern; E2609 has not shown a deleterious effect on sperm in preclinical reproductive toxicity studies. | • Synopsis:<br>o Exclusion Criteria<br>• Section 9.3.2 |
| Added option for subjects who provided a CSF sample prior to randomization but who declined the CSF sample collection after 4 weeks of dosing to provide a postdose CSF sample at any point in the study (ie, even after 4 weeks of dosing). | Reflects the added value of CSF data for the PK/PD secondary objective of this study. In addition, given that PK steady state is achieved within the 1st 2 weeks of initiation of dosing, data collected post Week 4 visit is still considered to be applicable in assessment of the steady state effect. | • Synopsis -<br>o Pharmacodynamic Assessments<br>• Section 5.3<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.5.1.3.3<br>• Section 9.5.1.4<br>• Table 6<br>• Table 7<br>• Table 8 |
| Revised details of restrictions to anticoagulant therapy and short-term steroid use revised/moved details regarding antiplatelet drugs to the main body of the protocol | To assist in subject recruitment and retention and considering that the strict restrictions were not necessary for subject safety | • Synopsis -<br>o Concomitant Drug/Therapy<br>• Section 9.4.7<br>• Appendix 2 |
| Removed the >33% decrease from baseline for CD4, CD8, and CD19 as a trigger for more frequent testing of flow cytometry and CBCs. Additional safety monitoring for CD4, CD8, CD19, and CBCs will only be based on the population adjusted LLNs for clinically asymptomatic subjects. | Experience to date has indicated significant variability within the normal range, both for increases and decreases. Absolute counts of lymphocyte subsets are more meaningful than percentage decreases for triggering more frequent monitoring. | • Section 9.3.3<br>• Table 1<br>• Table 2 |

**Revisions to Version 5.0**

**New version/date: Version 6.0 / 29 Jun 2016 (per Amendment 04)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Added option to temporarily suspend study drug for subjects who are clinically asymptomatic but who meet CD4, CD8, or CD19 discontinuation thresholds on 2 consecutive tests. Introduce rules for ability to re-start study drug (ie, rechallenge) in these subjects. Only 1 cycle of temporary suspension and rechallenge with study drug permitted for any individual subject. | To assist in subject retention and to gain knowledge on the behavior of lymphocyte subsets on rechallenge. | • Section 9.3.3<br>• Table 1<br>• Table 2 |
| Added extra blood draw times with focus on lymphocyte subsets, CBCs, and immunoglobulins during the 12-week safety follow-up for all subjects. | To increase frequency of key safety monitoring parameters in post-treatment follow-up period so as to assess immunological changes after completion of study drug | • Synopsis<br>o Study Design<br>o Safety Assessments<br>• Section 9.1.2.2<br>• Section 9.1.2.3<br>• Section 9.2.5<br>• Section 9.3.3<br>• Table 7<br>• Table 8<br>• Section 9.5.1.5.7<br>• Section 9.5.5 |
| Clarified that the Functional Assessment Questionnaire is to be administered to the informant/caregiver, and not the subject. | Clarification | • Synopsis<br>o Efficacy Assessments<br>• Section 9.5.1.3.1 |
| Added clarification that the Brief Smell Identification Test will be administered as part of the neurological examination | Clarification | • Synopsis<br>o Safety Assessments<br>o Interim Analyses<br>• Section 9.1.1.2<br>• Section 9.5.1.2.1<br>• Section 9.5.1.5.9<br>• Table 6<br>• Table 7 |

**Revisions to Version 5.0**

**New version/date: Version 6.0 / 29 Jun 2016 (per Amendment 04)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised number of randomized subjects in Stage A to n=60±20% | To allow for additional randomization based upon current number of subjects in screening at the time of amendment implementation | • Synopsis<br>  ○ Study Design<br>  ○ No. of Subjects<br>• Section 7<br>• Section 9.1<br>• Section 9.2.1<br>• Section 9.2.5<br>• Section 9.3<br>• Section 9.7.3 |
| Grammatical, typographical, and formatting corrections | Consistency | various |

**Revisions to Version 4.0**

**New version/date: Version 5.0, 06 Feb 2016 (per Amendment 03)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Add interim analyses of safety, and PK/PD data throughout Stage A | Decision making regarding the remainder of the study and the full E2609 clinical development program | • Synopsis –<br>o Exploratory Endpoint Analysis<br>o Interim Analysis<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.4.6<br>• Section 9.7.1.7.1 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Grammatical, typographical, and formatting changes | | Throughout |
| Mandatory nature of CSF collection in study changed to voluntary. This change impacts the timing and details of the PK/PD interim analyses. It also impacts the nature of the CSF-related objectives, which will now be identified as exploratory. | To increase rate of subject consent into the study | • Synopsis –<br>o Secondary Objectives<br>o Exploratory Objectives<br>o Study Design<br>o Exclusion Criterion No. 12<br>o Pharmacokinetic Assessments<br>o Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments<br>o Safety Assessments<br>o Secondary Endpoints<br>o Exploratory Endpoints<br>o Analysis for the Secondary Endpoints<br>o Analysis for the Exploratory Endpoints<br>• Section 5.3<br>• Section 8.2<br>• Section 8.3<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.2.5<br>• Section 9.3.2<br>• Section 9.4.6<br>• Section 9.5.1.3.3<br>• Section 9.5.1.4<br>• Section 9.5.1.5.12<br>• Section 9.7.1.1.2<br>• Section 9.7.1.1.3<br>• Section 9.7.1.6.2<br>• Section 9.7.1.6.3<br>• Appendix 2, Listing 2 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Extended the range of cognitive impairment in delayed recall that would be considered inclusionary for the study and removed the eligibility nature of the cognitive tests repeated at the Baseline Visit. | Original delayed recall aspect of inclusion criterion #1 was considered to be too restrictive and was unnecessarily screening out subjects with MCI/prodromal AD. The eligibility nature of the cognitive tests repeated at the Baseline Visit has been removed in order to simplify the requirements of the pretreatment period for the study. | • Synopsis –<br>○ Inclusion/ Exclusion Criteria<br>• Section 9.3.1<br>• Section 9.3.2 |
| Addition of historical amyloid PET scans for determination of eligibility for the study. Subjects with historical PET scans will not be part of the longitudinal PET analyses and therefore will not require a second PET scan at either Visit 18 or ED. | To provide the sites with greater operational flexibility and reduce subject burden. | • Synopsis –<br>○ Inclusion/Exclusion<br>○ Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments<br>• Section 9.1.1<br>• Section 9.2.4.3<br>• Section 9.3.1<br>• Section 9.5.2<br>• Table 6<br>• Table 7 |
| Added the need for safety laboratory tests to be repeated for subjects whose pre-treatment period is extended due to active infection. | To ensure that all baseline safety laboratory tests are repeated for subjects whose pretreatment period is extended. | • Synopsis –<br>○ Inclusion/Exclusion<br>• Section 9.3.2<br>• Section 9.5.2<br>• Table 6 |
| Clarified that exclusion criterion No. 22 (exclusion of subjects with CD4, CD8, or CD19 absolute counts below the LLN) applies to flow cytometry tests conducted at both the Screening and the Baseline Visits. Furthermore, LLNs that are adjusted for the subject population under study will be used. | It was not clear that Exclusion Criterion No. 22 applied to both the Screening and the Baseline Visits. The LLNs for CD4, CD8 and CD19 absolute counts require adjustment for the age of the patient population in this study. | • Synopsis –<br>○ Inclusion/ Exclusion Criteria<br>• Section 9.3.2 |
| Provided additional detail | Added to provide clarity | • Synopsis – |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| regarding scope of Exclusion Criterion No. 34 which excludes subjects with hypopigmentation conditions. | for the sites. | ○ Exclusion Criteria<br>• Section 9.3.2 |
| Revised number of clinical sites from 30 to 40 | For feasibility purposes | • Synopsis –<br>○ Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Relaxed the requirement for the cognitive assessments at Screening Visit 1 to be conducted in a certain order and revised the recommended order in which the assessments could be conducted. | To provide the sites with greater operational flexibility. | • Section 9.1.1<br>• Figure 2<br>• Section 9.5.1.3.1<br>• Section 9.5.2<br>• Table 6 |
| Clarify the duration for which the Safety magnetic resonance imaging (MRI) scan, the amyloid PET scan and the lumbar puncture (LP) collected CSF conducted at Screening are considered valid. | To provide sites with greater operational flexibility, particularly for re-screening of screen fail subjects. | • Section 9.1.1 |
| Clarify that for subjects meeting criteria for weekly monitoring of lymphocyte subsets, these can be accommodated within the scheduled clinic visits during the early stages of the treatment period of the study. | To provide operational clarity to the sites. | • Synopsis –<br>○ Exclusion Criteria<br>• Section 9.3.2<br>• Section 9.3.3<br>• Section 9.5.1.5.3 |
| Added the requirement for complete blood counts (CBC) with differentials to be performed whenever repeat or unscheduled flow cytometry tests are performed. | Such that CBC data are available at all times when flow cytometry data is available. | • Section 9.3.3<br>• Table 1<br>• Section 9.5.2<br>• Table 6<br>• Table 7 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Added 30 day window to the duration of the pre-treatment period if required for medical or operational reasons. | To provide the sites with greater operational flexibility. | • Synopsis –<br>  ○ Study Design<br>  ○ Duration of Treatment<br>• Section 9.1<br>• Figure 1<br>• Section 9.1.1<br>• Section 9.1.1.2<br>• Section 9.5.2<br>• Table 6 |
| Clarified the timing of the start of the Randomization Phase | Clarification | • Section 9.1.1<br>• Section 9.1.2<br>• Section 9.5.2<br>• Table 6<br>• Table 7 |
| Increased number of MCI/Prodromal or mild to moderate AD subjects screened for entry into the study | To reflect the higher screen failure rate than originally anticipated | • Synopsis –<br>  ○ Number of Subjects |
| Removal of CD127 cell surface markers | FoxP3 is the most accepted marker to measure T regulatory cells and additional assessment of CD127 is not required. | • Section 9.5.1.5.3<br>• Table 4<br>• Section 9.5.2.1 |
| Made the clinical biochemistry, urinalysis, CBC, lymphocyte subsets, and immunoglobulin tests mandatory at Visit 20, regardless of clinical significance at Visit 19. | For more comprehensive safety data at the second follow-up visit. | • Section 9.5.2<br>• Table 7 |
| Corrected reference to Exclusion Criterion No. 20 (and not to Exclusion #19) in footnote to Table 6 and Table 7 regarding timing of Visit 3 in relation to Visit 2. | Correction | • Section 9.5.2<br>• Table 6<br>• Table 7 |
| Revised details regarding prohibited antiplatelet drugs | To distinguish between those subjects who consent to CSF sample collection and those who do not | • Appendix 2, Listing 2 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015 (per Amendment 01)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised inclusion to allow for enrollment of mild to moderate AD subjects in Stage A and expand the Stage B mild AD cohort to also include moderate AD subjects | To collect safety data in a wider range of AD patients. | • Title Page<br>• Synopsis –<br>  ○ Objectives<br>  ○ Study Design<br>  ○ Number of Subjects<br>  ○ Inclusion/Exclusion Criteria<br>  ○ Study Treatments<br>  ○ Efficacy Assessments<br>  ○ Study Endpoints<br>  ○ Efficacy Analyses<br>  ○ Interim Analyses<br>  ○ Adaptive Randomization<br>  ○ Sample Size<br>• Section 5.3<br>• Section 7<br>• Section 8 (and all subsections)<br>• Section 9.1<br>• Section 9.1.1<br>• Figure 1<br>• Section 9.2.1<br>• Section 9.2.2<br>• Section 9.2.3<br>• Section 9.2.4.3<br>• Section 9.2.4.4<br>• Section 9.3<br>• Section 9.3.1<br>• Section 9.3.2<br>• Section 9.4.1<br>• Section 9.4.3<br>• Section 9.4.4<br>• Section 9.5.1.3.1<br>• Section 9.7.1.1.2<br>• Section 9.7.1.1.3<br>• Section 9.7.1.4<br>• Section 9.7.1.6<br>• Section 9.7.1.6.2<br>• Section 9.7.1.6.3<br>• Section 9.7.1.8.2<br>• Section 9.7.3<br>• Section 9.7.4 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015 (per Amendment 01)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised inclusion criteria for MMSE to ≥16 from ≥20 | The MMSE score is used as a cut-off for the most impaired subject that would be eligible for the study. Lowering the MMSE inclusion from ≥20 to ≥16 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD cohort. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.1 |
| Revised inclusion criteria for FAQ to ≤24 from ≤20 | As for the MMSE, the FAQ score is used as a cut-off for the most impaired subject that would be eligible for the study. Revising the FAQ inclusion from ≤20 to ≤24 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD cohort, and is consistent with an MMSE inclusion of ≥16. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.1 |
| Revised exclusion criteria such that small arachnoid cysts are not necessarily exclusionary | Arachnoid cysts are a common finding in otherwise healthy subjects. Small lesions (<1 cm in diameter) are generally not considered clinically significant and if discovered incidentally no long term follow up is routinely required. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised exclusion criteria for Ig (IgG, IgA, or IgM) to specify that levels below the LLN at Screening or Baseline need not be exclusionary | For subjects with a Screening or Baseline IG level <LLN to be considered for continuation in the study, assessment of clinical significance of the finding will be required. A finding of "not clinically significant" must be agreed between the Investigator and Medical Monitor in order for the subject to continue in the study. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised text to provide instructions for subject assent and associated consent by a legal representative for subjects who the Investigator considers not to have the capacity to consent themselves | With the expansion of the patient population to include moderately demented subjects it was necessary to provide directions regarding the consenting process for subjects considered to be lacking the | • Section 5.3 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015 (per Amendment 01)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | capacity to consent themselves. | |
| Revised number of clinical sites to 30 from 25 | For feasibility purposes. | • Synopsis –<br>  ○ Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Added allowance for Tier 1 and Tier 2 screening assessments to be performed on the same day | Added to provide operational clarity for the sites. | • Section 9.1.1.1<br>• Table 6 |
| Removed requirements for MRIs to include sequences for resting state functional MRI | This was an error and should not have been included in the original protocol. | • Table 6<br>• Table 7 |
| Revised text to clarify that on visits where CSF collection takes place, the CSF collection need not take place on the same day as the cognitive testing for that visit | Added to provide operational clarity for the sites. | • Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised text to clarify that the most important efficacy assessment to keep blinded from safety data is the CDR. | Added to provide operational clarity for the sites. | • Synopsis –<br>  ○ Safety Assessments<br>• Section 9.4.6<br>• Section 9.5.1.5 |
| Revised text to allow PK blood sample and PD blood samples to be taken either shortly before or shortly after the LP on CSF days | Added to provide operational flexibility for the sites. | • Section 9.5.1.4.1<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised Sponsors Grading for Laboratory Values for the following analytes: lymphocytes, neutrophils, albumin, creatinine, phosphate, and potassium serum-high (hyperkalemia) | Corrections made to align with the values for grading used by the central clinical laboratory for this study. | • Appendix 1 |
| Revised details regarding prohibited antiplatelet drugs | Previous version incorrectly referenced a biomarker subgroup. All subjects in this study will need to provide CSF samples. | • Appendix 2; Listing 2 |
| Revised grammar, spelling, etc. | Compliance with current company style guide and for general consistency. | Throughout protocol |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revisions to grammar, spelling, etc. | Compliance with current company style guide and for general consistency | • Throughout protocol |
| Revisions made per new company protocol template | Alignment with current Eisai template | • Synopsis –<br>  ○ Inclusion/Exclusion Criteria<br>• Section 9.1.2.3<br>• Section 9.3.1<br>• Section 9.3.2<br>• Section 9.5 (related subsections)<br>• Section 9.5.4<br>• Section 9.5.4.1<br>• Section 9.5.4.2<br>• Section 9.5.4.3 |
| Clarified classification of MCI due to AD | Clarification that MCI due to AD population will also be consistent with the research criteria for Prodromal AD in that impaired episodic memory is required and will be tested using a list learning task (the International Shopping List Task) | • Synopsis –<br>  ○ Study Design<br>• Section 9.1 |
| Replaced "enroll" with "randomize," pertaining to subject entry into study | Correction to terminology | • Synopsis –<br>  ○ Study Design<br>• Section 9.1<br>• Section 9.3 |
| Added criterion excluding subjects with hepatic impairment and total bilirubin greater than 1.5×ULN or INR greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded. | At request of FDA, exclude subjects who have hepatic impairment | • Synopsis –<br>  ○ Inclusion/Exclusion Criteria<br>• Abbreviation List<br>• Section 9.3.2 |
| Added coagulation parameters for prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR) to screening and baseline procedures | Screen for hepatic impairment | • Synopsis –<br>  ○ Inclusion/Exclusion Criteria<br>• Abbreviation list<br>• Section 9.3.2<br>• Table 4<br>• Table 6<br>• Table 8 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| For subjects who discontinue study drug prematurely, conduct efficacy assessments postdose at same time points as subjects who continue in the study. Added FAQ to this set of efficacy assessments. | To facilitate efficacy analyses, which are based on longitudinal modeling for all subjects | • Synopsis –<br>○ Study Design<br>• Section 9.1.2.2<br>• Section 9.3.3<br>• Section 9.5.4.1<br>• Section 9.5.5<br>• Table 7 |
| Delete diagram of E2609 structure | This display is not needed for the protocol. The Investigator's Brochure has this information. | • Section 9.4.2.1 |
| Additional blood samples to be taken at Visits 19 and 20 | Samples are to be put in storage to allow for assessment of immune status at end of study, as needed. | • Synopsis –<br>○ Assessments<br>• Table 8 |
| Add subheadings to Section 9.7 describing the primary endpoint analysis, and text clarifying that no multiplicity adjustments will be done to account for the interim analyses | To distinguish clearly the primary analysis and the sensitivity analyses of the primary endpoint | • Synopsis –<br>○ Efficacy Analyses<br>• Section 9.7.1.6.1 |
| Clarification of PK sampling upon Early Discontinuation | Additional operational details of the timing of the PK sampling at the ED visit provided | • Section 9.5.1.4.1<br>• Table 7 |
| Clarification of ApoE testing | Clarification that the ApoE genetic testing will be for homozygous or heterozygous E4, versus non-E4 | • Section 9.5.1.4.2 |
| Revision to PK/PD interim analysis text | Confirm that interim PK/PD analysis will be conducted by an independent group | • Section 9.4.6 |
| Addition of text regarding safety signals with E2609 | To provide information on safety-driven dose adjustments | • Synopsis –<br>○ Study Design<br>• Section 9.1 |
| Addition of PBMC collection/assessment at Baseline, during treatment, and post-treatment | Recent animal studies have shown an effect of E2609 on this model so they will be added to the 202 clinical study as an additional exploratory assessment. | • Synopsis –<br>○ Safety Assessments<br>• Section 9.2.5<br>• Section 9.5.1.5<br>• Table 4<br>• Table 6<br>• Table 7<br>• Table 8 |
| Stipulate that exploratory biomarker analyses may be conducted using blood or CSF samples that may have been drawn for other purposes | To allow more flexibility for possible exploratory biomarker studies associated with study drug or disease, including miRNA and DNA | • Synopsis –<br>○ Assessments<br>• Abbreviation list<br>• Section 9.5.1.4.2<br>• Section 9.5.1.5.12<br>• Table 6 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | | • Table 7 |
| Prohibit concomitant medications that are strong CYP3A4, inhibitors, but clarify that no restrictions are needed for other CYP3A4 inhibitors, CYP3A4 inducers, or CES2 inhibitors | At request of FDA, in light of finding that inhibition of CYP3A4 by a reference agent increases plasma levels of E2609 | • Synopsis –<br>○ Concomitant Drug/Therapy<br>• Section 7.1<br>• Section 9.4.7<br>• Appendix 2, Listing 6 |
| Addition of tests for viral characterization at Baseline | To confirm by serology information of subjects prior exposure to common viruses pre-dosing with study drug | • Section 9.5.1.2.2<br>• Table 4<br>• Table 6<br>• Table 8 |
| Use of a centralized dermatologist assessment via photography | A centralized approach, using standardized photography, to FDA-required serial dermatological assessments will be employed for consistency of assessments between sites and for consistency of longitudinal assessments of individual subjects. | • Synopsis –<br>○ Safety Assessments<br>• Section 9.2.5<br>• Section 9.5.1.5<br>• Section 9.5.1.5.8<br>• Table 6<br>• Table 7 |
| Removal of testing for benzodiazepines or opioids as part exclusion criteria #35 | To differentiate appropriate medicinal use from recreational drug use or abuse | • Synopsis –<br>○ Exclusion Criteria<br>• Section 9.3.2 |
| Addition of analysis of other covariates such as adjusted hippocampal volume will be studied | Hippocampal volume has been shown to correlate with rate of cognitive decline and as such is a key covariate to be used in the analyses. | • Synopsis –<br>○ Analysis of Primary Endpoint<br>• Section 9.7.1.6.1 |
| Addition of clarifications to ophthalmic examination | To provide more detail around the requirements for the ophthalmic exam | • Synopsis –<br>○ Safety Assessments<br>• Section 9.5.1.5.13<br>• Table 6<br>• Table 7 |
| Addition of details regarding specific method of CSF collection (ie, gravity drip) | Use of materials required for suction method when collecting CSF can affect the PD data and so it is important to make it clear that only the gravity drip method can be used for collecting CSF in this study for protecting the quality and the consistency of the CSF PD data. | • Section 9.5.1.3.3<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Addition of specific testing for B12 levels at Screening | Abnormally low serum vitamin B12 levels are exclusionary for the study (exclusion criterion 8) but a | • Synopsis –<br>○ Exclusion Criteria<br>• Section 9.3.2 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | blood draw for Vitamin B12 was inadvertently missed out of Table 6 in protocol version 1. | • Section 9.5.1.2.3<br>• Figure 2<br>• Table 6 |
| Addition of details regard AEs that might be signals of possible drug abuse potential | Changed terminology re: collection of additional information for AEs that might be signals of possible abuse potential. No longer use the word "narrative" in order to avoid potential confusion with standard clinical trial narratives eg, for serious adverse events, adverse events leading to withdrawal, etc. | • Synopsis –<br>○ Safety Assessments<br>• Section 9.2.5<br>• Section 9.5.1.5.1<br>• Appendix 4 |
| Addition of clarification regarding position for taking vital signs (ie, supine) | The American Heart Association guidelines only mention supine, standing, and sitting as positions for taking HR and BP measurements. Therefore, have changed required position from semi-supine to sitting. | • Section 9.5.1.5.4<br>• Table 6<br>• Table 7 |
| Stipulated that study drugs are to be taken with food | For consistency of treatment conditions | • Section 9.5.1.4.1 |
| Change to list of Study Specific AEs which should be considered SAEs | Eisai's standard procedures have changed such that non-serious study specific adverse events of interest are no longer reported to Eisai Product Safety; instead, any additional information required for such non-serious adverse events will be obtained through other methods. In addition, certain events (new onset seizures, ocular herpes) are now to be classified as serious as important medical events, regardless of whether they meet standard ICH serious criteria. | • Section 9.5.1.5.1<br>• Section 9.5.1.5.2 |
| Increased blood volume for PK | To match collection tubes and ensure sufficient sample for planned assays | • Table 8 |
| Corrected error in definition of PK analysis set | For accuracy | • Synopsis –<br>○ Study Endpoints<br>• Section 9.7.1.2 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Addition of details regarding discontinuation of study drug | To clearly and consistently differentiate "discontinuation from study drug" from "withdrawal from study" | • Synopsis<br>• Section 7<br>• Section 9.1.2.1<br>• Section 9.2.5<br>• Section 9.3.3<br>• Table 1<br>• Table 2<br>• Section 9.4.1<br>• Section 9.4.4<br>• Section 9.5.1.5.1<br>• Section 9.5.1.5.3<br>• Section 9.5.5 |
| Re-ordered prohibited medication lists | For consistency, all lists re-ordered in alphabetical order of generic drug name, and footnotes revised for overall consistency | • Appendix 2 |
| Moved nefazodone from Listing 9 to Listing 6 | Nefazodone is a strong CYP3A4 inhibitor and is therefore prohibited. | • Appendix 2 |

# 1 TITLE PAGE


## Clinical Study Protocol

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01 and 05) |
| **Sponsor:** | Eisai Inc.<br>100 Tice Boulevard<br>Woodcliff Lake,<br>New Jersey 07677<br>United States<br><br>Eisai Ltd.<br>European Knowledge Centre<br>Mosquito Way<br>Hatfield, Hertfordshire<br>AL10 9SN<br>United Kingdom<br><br>Eisai Co., Ltd.<br>4-6-10 Koishikawa<br>Bunkyo-Ku,<br>Tokyo 112 8088<br>Japan |
| **Investigational Product Name:** | E2609 |
| **Indication:** | Alzheimer's disease |
| **Phase:** | 2 |
| **Approval Date:** | V1.0 15 Jul 2014 (original protocol)<br>V2.0 21 Oct 2014 (revised original protocol)<br>V3.0 28 May 2015 (Amendment 01)<br>V4.0 05 Nov 2015 (Amendment 02)<br>V5.0 06 Feb 2016 (Amendment 03)<br>V6.0 29 Jun 2016 (Amendment 04)<br>V7.0 26 Sep 2016 (Amendment 05)<br>V8.0 02 Nov 2016 (Amendment 06) |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |
| **GCP Statement:** | This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities. |
| **Confidentiality Statement:** | This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study. |

# 2 CLINICAL PROTOCOL SYNOPSIS

**Compound No.:**
E2609

**Name of Active Ingredient:**
*N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

**Study Protocol Title**
A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01 and 05)

**Investigators**
Investigators in the United States only (revised per Amendment 05)

**Sites**
Approximately 35 sites, United States only (revised per Amendments 01, 02, 04, and 05)

**Study Period and Phase of Development**

— Approximately 32 months (revised per Amendment 05)

— Phase 2

**Objectives**

**Primary Objective** (revised per Amendment 05)

- To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with Mild to Moderate Dementia due to Alzheimer's Disease (referred to as mild to moderate AD throughout the protocol) (revised per Amendment 01)

**Secondary Objectives** (revised per Amendments 02 and 05)

- To characterize the plasma and cerebrospinal fluid (CSF) pharmacokinetics (PK) of E2609
- To assess the effects of E2609 on Aβ(1-x) and Aβ(1-42) in CSF from 4 weeks and up to 18 months of treatment

**Exploratory Objectives**

(revised per Amendments 01, 02, 04, and 05)

- To explore the effects of E2609 on CSF Aβ(1-40) and beta (β)-amyloid converting enzyme 1 (BACE1) measurements from 4 weeks and up to 18 months of treatment
- To explore the effects of E2609 compared with placebo on various biomarkers. Biomarkers to be explored may include but are not limited to:
    a. CSF biomarkers of neurodegeneration (eg, total tau [t-tau], phosphorylated-tau [p-tau]) after 18 months of treatment
    b. Plasma and CSF amyloid, and CSF BACE1 measurements from 4 weeks and up to

18 months of treatment (revised per Amendment 06)

c. Total hippocampal atrophy at 12 and 18 months of treatment, as measured by volumetric magnetic resonance imaging (vMRI)
d. vMRI measurements including left and right hippocampal volume, whole brain volume and total ventricular volume at 6, 12, and 18 months of treatment
e. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)

- To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during posttreatment follow-up, by assessment of:
  a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog$_{14}$)
  b. The Clinical Dementia Rating (CDR) scale
  c. The Mini-Mental State Examination (MMSE)
  d. The International Shopping List Task (ISLT)
  e. The CogState Brief Battery (CBB)
  f. The Functional Assessment Questionnaire (FAQ; also known as the Functional Activities Questionnaire)
- To explore the relationship between the treatment effects of E2609 on measured clinical efficacy scales (eg, MMSE, CDR) and its effects on CSF amyloid, CSF amyloid isoforms, brain amyloid, and vMRI
- To explore relationships between both E2609 dose and exposure, with pharmacodynamic (PD) and safety endpoints

**Study Design**

This will be a multicenter, placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild to moderate AD. A common set of inclusion criteria, consistent with the National Institute on Aging–Alzheimer's Association (NIA-AA) clinical research criteria for Mild Cognitive Impairment (MCI) due to Alzheimer's Disease (AD) or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with the criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study consists of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days, plus an additional window of up to 30 days if required [revised per Amendment 02]) includes a Screening Visit (Visit 1) and a Baseline Visit (Visit 2). All screening assessments (within 4 distinct tiers) must be completed, and eligibility to continue in the study confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

The study will be limited to approximately 35 sites in the United States. (revised per Amendments 01, 02, and 04) Subjects will initially be randomized 1:1:1:1 to 4 treatment groups (5, 15, or 50 mg

E2609 or placebo) within each of the 2 clinical populations. (revised per Amendments 01, 04, 05, and 06) In addition to the placebo group, 3 E2609 doses will be used to reduce CSF amyloid β levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/pharmacodynamic (PD) modeling has shown that these doses should achieve these targets when administered once daily (QD) with food, and these doses will be evaluated based on the 4-week (or later) assessment of CSF Aβ(1-x) from subjects who provide voluntary consent for CSF measurement. (revised per Amendment 02) Upon implementation of Amendment 06, at the next regularly scheduled visit, subjects receiving E2609 5 or 15 mg who have not yet completed Visit 17 (Week 66), will be re-assigned in a blinded manner to E2609 50 mg for the remainder of the double-blind treatment period. In order to maintain the blind, all subjects who have not yet had Visit 17 will go through the same procedures with the placebo-randomized subjects continuing to receive placebo and those randomized to E2609 50 mg continuing to receive 50 mg. (revised per Amendment 06)

Safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the 1st subject is randomized into the study through the time the last subject is randomized, an independent data safety monitoring board (DSMB; including at least 1 immunologist) will review all safety data in an unblinded manner. (revised per Amendment 06) The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. (revised per Amendments 01, 04, and 05)

Interim analyses of the E2609 plasma PK for all subjects and the E2609 CSF PK and PD profiles will be performed on baseline data and samples collected after at least 4 weeks of treatment. (revised per Amendment 05) These interim analyses, as well as analyses of safety data, will be performed on an ongoing basis throughout the study. Refer to the Interim Analysis section for more detail. These data will be used to evaluate the CSF PD effects of E2609 doses, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels. (revised per Amendments 01 and 02) The median and mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks or more of treatment for each dose of E2609 and the 90% confidence interval (CI) for the median will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data and will relate the average steady state plasma concentration of E2609 to CSF Aβ(1-x) percentage reduction from baseline determined after at least 4 weeks of dosing. (revised per Amendments 01, 02, 03, 04 and 05)

Once subjects have completed at least 12 weeks of treatment (or discontinued study drug early) an interim safety analysis will be conducted by Eisai and the DSMB. At the completion of this interim safety review, the frequency of subsequent unblinded safety reviews will be re-evaluated by the DSMB and the Sponsor and this information will be provided in the DSMB charter. (revised per Amendment 06) Subjects will continue study drug while the DSMB reviews all the available safety data. (revised per Amendments 01, 04, and 05). (revised per Amendment 06)

**Early Discontinuation**

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug. (revised per Amendments 04 and 05)

**Follow-Up**

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 4 post-treatment Follow-Up Visits: 2, 4, 8, and 12 weeks after the last dose of study drug. If clinically indicated, more frequent safety assessments can be conducted as

part of unscheduled visits during the post-treatment Follow-Up Period. (revised per Amendment 04)

**Number of Subjects**

Approximately 400 MCI/Prodromal or mild to moderate AD subjects will be screened to provide approximately 60 (±20%) randomized subjects (a target of approximately 15 subjects per treatment arm). There will be no limit to the number of subjects randomized from either clinical cohort. (revised per Amendments 01, 02, 04, and 05)

**Inclusion Criteria**

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD or AD dementia and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at Screening Visit 1:**
(revised per Amendment 02)

   a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation
   b. Cognitive impairment of at least 1 standard deviation (SD) from age adjusted norms in delayed recall on the ISLT. Alternatively, cognitive impairment of at least 0.5 SD from age-adjusted norms in delayed recall on the ISLT plus impairment of at least 1 SD from age-adjusted norms in at least 1 other computerized learning and memory test (ISLT immediate recall, or 1 of the learning and memory components of the CBB). (revised per Amendment 02)
   c. FAQ ≤24 (revised per Amendment 01)
   d. MMSE ≥16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading; an historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group (revised per Amendment 02)
3. Male or female, age 50 to 85 years, inclusive at time of consent
4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.
5. If receiving acetylcholinesterase inhibitors (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study

but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.

Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization.

**Exclusion Criteria (revised per Amendment 04)**

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or magnetic resonance imaging (MRI)
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and <1 cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could, in the opinion of the investigator, confound the MCI/Prodromal or mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendments 01 and 02)
7. A score of ≥8 on the 15-item Geriatric Depression Scale at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the lower limit of normal (LLN) for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
12. Any contraindications to lumbar puncture (LP) for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to

obesity). Only applicable to subjects consenting to CSF sample collection (revised per Amendment 02)

13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization
20. Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below population-adjusted LLN at Screening or Baseline and confirmed by a repeat test conducted 1 week after the initial test. The population-adjusted LLN for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are 396, 157, and 74 cells/μL respectively. (revised per Amendment 02)
23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the Investigator and the Medical Monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of clinical immunodeficiency. The discussion with the Medical Monitor should include a detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)
24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate electrocardiograms (ECGs). A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT

Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.

26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute at Screening or Baseline
29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.
33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo). Diagnosis of an underlying disease causing hypopigmentation is not necessary for exclusion if the clinical presentation is consistent with such a condition. Hypopigmentation associated with scarring need not be exclusionary. (revised per Amendment 02)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within

60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent

41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the 1st dose of study drug.
43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period and for 28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.
    - Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
      (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

**Study Treatments**

E2609 tablets of 5-, 10-, and 25-mg dose strengths will be supplied. Placebo tablets to match E2609 will be of identical appearance. Each subject will receive 2 tablets, which when combined will make up the required doses of E2609 or placebo, to be administered orally QD with food. (revised per Amendment 05)

**Duration of Treatment**

The maximum duration of a subject's participation in the study will be approximately 2 years, comprising:

- Screening and Baseline Periods (Prerandomization Phase): up to 60 days, plus an additional window of up to 30 days if required (revised per Amendment 02)

  (In subjects who have an active infection within 4 weeks of the planned randomization date, the duration of the pre-randomization phase can be extended by up to 4 weeks to allow additional time for resolution of the infection.)
- Treatment Period (Randomization Phase): up to 78 weeks
- Follow-Up Period (Randomization Phase): 12 weeks (post last dose)

**Concomitant Drug/Therapy**

(revised per Amendment 04)

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit (see Appendix 2 for a detailed listing of these agents):

- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization. However, during the treatment period of the study, short term (not more than 14 days) use of steroids up to the equivalent of prednisolone 40 mg QD is permitted after discussion with the Medical Monitor. Dosing with study drug should be suspended from the time steroid treatment is started. Complete blood count and lymphocyte subsets should be determined prior to starting steroid treatment and continue to be monitored weekly. Study drug may be resumed after discussion with the Medical Monitor when the following conditions are met: (1) treatment with steroids has been completed for at least 1 week; (2) total lymphocytes not <LLN; (3) no lymphocyte subsets are below the discontinuation threshold; (4) the investigator considers that the medical condition which required treatment with steroids has improved or resolved. Weekly testing of lymphocyte subset counts and CBC with differentials is required for 4 weeks following resumption of study drug administration. (revised per Amendment 04)
- (revised per Amendment 06)

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for any efficacy analyses. (revised per Amendment 05)

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed. Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before randomization. They may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 04)
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if, in the opinion of the investigator, this will not interfere with study procedures or subject safety, and are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive

function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks

Antiplatelet therapy: (revised per Amendment 04)

- For subjects who consent to CSF sample collection: Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) are permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.
- For subjects who do not consent to CSF sample collection: Aspirin and clopidogrel, individually or in combination, are permitted.

**Assessments**

**Efficacy Assessments**

Alzheimer's Disease Assessment Scale - cognitive subscale: The 14-item version will be used since it is considered more relevant for subjects with MCI/Prodromal AD or mild AD.

Clinical Dementia Rating: Assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

Mini-Mental State Examination: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing.

International Shopping List Task: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall.

CogState Brief Battery: A computer-based battery comprising 4 cognitive tests:

- Detection – a simple reaction time test. Speed of response is the measure.
- Identification – a simple choice reaction time test. Speed of response is the measure.
- One Card Back – a simple working memory test. Accuracy of response is the measure.
- One Card Learning – a visual learning and memory test. Accuracy of response is the measure.

Functional Assessment Questionnaire: The FAQ has 10 items concerned with performing daily tasks necessary for independent living. The caregiver or informant provides performance ratings on 10 complex activities of daily living performed within the preceding 4 weeks. (revised per Amendment 04)

Volumetric Magnetic Resonance Imaging: vMRI will be used to evaluate disease modification, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs.

**Pharmacokinetic Assessments**

Blood samples will be collected for the determination of the concentrations of E2609. For subjects who consent to CSF sample collection, CSF samples will be collected for the determination of E2609 concentrations. (revised per Amendment 02) Analyses of metabolite concentrations may be performed depending on emerging data from other studies with E2609.

**Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments**

Brain atrophy will be measured by vMRI: see Efficacy Assessments (above).

The soluble biomarkers Aβ(1-x), Aβ(1-42), (Aβ(1-40), total tau (t-tau), and p-tau will be measured in subjects who consent to CSF sample collection (revised per Amendment 02). BACE1 levels and

activity in CSF will also be measured in subjects who consent to CSF sample collection (revised per Amendment 02). Other exploratory biomarkers and amyloid isoforms (eg, Aβ[1-40]) may also be evaluated in plasma or CSF. (revised per Amendment 04) Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

Amyloid PET imaging will be used to confirm that all subjects eligible for progression to the Baseline Period have amyloid deposition in the brain. An historical amyloid positive PET scan may be used, if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02) Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses. (revised per Amendments 02 and 05)

Apolipoprotein E (*ApoE*) and N-acetyltransferase 2 (*NAT2)* genotyping/phenotyping will be conducted. *ApoE4* homozygous or heterozygous status versus non-carriers and *NAT2* status will be used in the statistical analysis to determine the effects on treatment response and safety. Remaining genomic DNA may also be stored for up to 15 years to be used to examine the role of DNA sequence variability on the absorption, distribution, metabolism, and elimination of E2609, development of adverse events (AEs), as well as the underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single-nucleotide polymorphisms with PK, safety, or PD data.

**Safety Assessments**

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR. (revised per Amendment 01) Routine safety assessments will include the monitoring and recording all AEs and serious adverse events (SAEs), monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

Complete blood counts and lymphocyte subset absolute counts and percentages will be measured (by a centralized laboratory) every week for the 1st month, every 2 weeks for the next 2 months (Months 2 and 3) and monthly for the next 3 months (Months 4, 5, and 6). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at all 4 Follow-Up Visits at 2, 4, 8, and 12 weeks after the last dose of study drug. Serum IgG, IgA, and IgM will be monitored monthly for the 1st 3 months, at 6, 12, and 18 months, and at the Follow-Up Visits that occur 4, 8, and 12 weeks after the last dose of study drug. (revised per Amendment 04)

Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and post-treatment for exploratory immunomodulatory and immune-based analyses.

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at baseline and at 3-month intervals during the Treatment Period. These assessments will specifically include evaluation of any areas of depigmentation or rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregivers/ informants will be instructed

to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so such AEs can be reviewed promptly.

Baseline and on-study blood and DNA samples will be taken and stored for all subjects, and CSF samples will be taken and stored for all subjects from whom CSF samples were collected (revised per Amendments 02 and 04). These samples may be tested for exploratory biomarkers associated with study drug or disease, or in the event that a subject develops AEs that warrant further investigation (eg, to test if a subject with a treatment-emergent infection was exposed to any suspected infective agents before treatment with study drug).

Safety brain MRI assessments will be performed at Screening, at 6, 12, and 18 months during the Treatment Period and at the final Follow-Up Visit. Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Full neurologic examinations will be performed at Baseline, at 6, 12, and 18 months, and at the 4- and 12-week Follow-Up Visits, by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. The neurologic examinations will include muscle strength testing and assessment of cranial nerves including olfaction, with the use of the Brief Smell Identification Test, as well as other parts of the CNS. (revised per Amendment 04)

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments will include the ADAS-$cog_{14}$, MMSE, and CBB.

An assessment of suicidality using the C-SSRS will be performed at Screening and Baseline and at regular intervals throughout the Treatment and Follow-Up Periods.

An ophthalmic examination (including retinal examination) will be conducted at Baseline. An additional examination will be conducted if the subject experiences visual disturbances during the course of the study.

A number of safety-related criteria for discontinuation of study drug are specified for the study.

**Bioanalytical Methods**

Plasma and CSF concentrations of E2609 will be measured by a validated liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) in both CSF and plasma will be measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendment 04)

BACE1 levels and activity may be measured using a customized assay. Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

**Statistical Methods**

All statistical tests will be based on the 5% (2-sided) level of significance. (revised per Amendment 05)

**Study Endpoints**

**Primary Endpoint**

- Safety and tolerability, which include incidence of treatment-emergent adverse events (TEAEs) and SAEs, laboratory parameters, vital signs, and ECG parameters (revised per Amendment 05)

**Secondary Endpoints**

(revised per Amendments 02 and 05)

- % reduction of Aβ(1-x) and Aβ(1-42) in CSF relative to baseline after at least 4 weeks and 18 months of treatment
- The population PK parameters of E2609 in CSF and plasma, including the effect of intrinsic and extrinsic factors (including NAT2 phenotype)

**Exploratory Endpoints**

(revised per Amendments 01, 02, 04, and 05)

Change from baseline in:

- CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months of treatment
- CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- CSF amyloid and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment (revised per Amendment 06)
- Total hippocampal volume at 12 and 18 months of treatment as measured by vMRI
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months as measured by vMRI
- Amyloid PET standardized uptake value ratio (SUVR) composite at 18 months for brain amyloid levels
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog$_{14}$, CDR, MMSE, ISLT, CBB, and FAQ

**Analysis Sets**

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose exploratory efficacy measurement. (revised per Amendment 05)
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least

1 post-treatment PD measurement.

**Efficacy and Biomarker Analyses** (revised per Amendment 05)

**Analysis for the Primary Endpoint**

There is no primary efficacy endpoint. (revised per Amendment 05)

**Analysis for the Secondary Endpoints**

An mixed-effects model with repeated measures (MMRM) will be used to analyze the following secondary endpoint:

- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) from 4 weeks and up to 18 months. Data from early discontinuations will also be included. (revised per Amendment 05)

**Analysis for Exploratory Endpoints**

(revised per Amendments 01, 02, 04, and 05)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months of treatment
- Change from baseline in CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Change from baseline in plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during post-treatment follow-up
- Change from baseline in CSF amyloid and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment (revised per Amendment 06)
- Change from baseline in total hippocampal atrophy at 12 and 18 months as measured by vMRI
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months as measured by vMRI
- Change from baseline in Amyloid PET SUVR composite at 18 months for brain amyloid levels

The following efficacy endpoints will be summarized using descriptive statistics:

- Change from baseline in the clinical assessments: ADAS-cog$_{14}$, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months

The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

**Pharmacokinetic Analyses**

The PK Analysis Set will be used for E2609 concentration listings and for summaries of E2609 concentrations in plasma and CSF by dose and day. E2609 metabolite PK data may also be listed and summarized. (revised per Amendment 05)

A population PK approach will be used to characterize the plasma PK of E2609. For this approach, plasma PK data from this study will be pooled with relevant data from Phase 1 studies. As appropriate, the effect of covariates on the PK of E2609 will be evaluated. The PK model will be parameterized for oral clearance (CL/F) and apparent volume of distribution (Vz/F) for E2609. Derived exposure parameters such as steady state area under the concentration time curve (AUC) and average concentration ($C_{avg}$) of E2609 and other derived parameters will be calculated from the

model using the individual estimates parameterized for oral clearance and dosing history. (revised per Amendment 04)

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). The percentage change from baseline in CSF Aβ(1-x), Aβ(1-40), Aβ(1-42), t-tau, p-tau, and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months will be analyzed and presented graphically. (revised per Amendments 04 and 05) Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status. Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels, amyloid load on PET, vMRI and E2609 dose, plasma and CSF exposure will be initially explored graphically and any emergent relationship will be explored through population PK/PD modeling. Additionally, the relationship between CSF exposure to E2609 and the change from baseline for 18 months in the ADAS-cog, the CDR, and the MMSE will be explored graphically. (revised per Amendments 04 and 05)

Additionally, the relationship between plasma exposures of E2609 and select lymphocyte parameters will be explored graphically, and any emergent relationship will be explored using population-based modeling methods. (revised per Amendment 04)

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. Further information is in the "Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments" section. Details of pharmacogenomic testing may be provided and reported separately.

**Safety Analyses**

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements, and cognitive decline assessment such as CBB will be summarized by treatment group using descriptive statistics. (revised per Amendment 05)

<u>Lymphocyte Subsets</u>

Lymphocyte subsets, including but not limited to, CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages]) and regulatory T cells will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose.

Serum IgG, IgM, IgA will be measured and summarized in the same manner as other laboratory parameters. (revised per Amendment 04)

**Interim Analyses**

In order to make decisions about the remainder of the study as well as the full E2609 clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. Investigators, other clinical site staff, subjects, caregivers/informants and study team will remain blinded to study treatment. (revised per Amendments 03 and 05)

An interim safety analysis will also be conducted when 60 subjects (±20%) have completed 12 weeks of treatment (or discontinue study drug early). (revised per Amendments 01, 03, 04, and 05)

**Stratification**

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

**Sample Size Rationale**

A total of 15 subjects per dose is deemed sufficient to derive adequate safety and PK/PD data to aid in the selection of appropriate doses and the design of the Phase 3 studies that may be planned subsequently. (revised per Amendment 04) Based upon the selection of the E2609 50-mg dose for the Phase 3 studies, subjects randomized to the active treatment arms will be re-assigned to the selected 50-mg dose for further evaluation. (revised per Amendment 06)

# 3 TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES



## LIST OF IN-TEXT FIGURES



## LIST OF APPENDICES

# 4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| Aβ | amyloid β |
| Aβ(1-x) | amyloid β (1-x) (ie, the amyloid β monomer from amino acid 1 to x [eg, 1-42]) |
| AChEI | Acetylcholinesterase inhibitor |
| AD | Alzheimer's disease |
| ADAS-cog | Alzheimer's Disease Assessment Scale - cognitive subscale |
| AE | Adverse Event |
| ApoE | Apolipoprotein E |
| AUC | area under the concentration x time curve |
| $AUC_{(0\text{-}24h)ss}$ | area under the concentration x time curve at steady state from time zero to 24 hours |
| BACE1 | Beta (β)-amyloid converting enzyme 1 |
| BP | blood pressure |
| bpm | beats per minute |
| CBB | CogState Brief Battery |
| CBC | complete blood count |
| CBP | childbearing potential |
| CDR | Clinical Dementia Rating |
| CES2 | carboxyesterase-2 |
| CFR | Code of Federal Regulations |
| $C_{max,ss}$ | maximum plasma concentration at steady state |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| CI | confidence interval |
| CRA | clinical research associate |
| CRF | case report form |
| CRO | contract research organization |
| CSF | cerebrospinal fluid |
| $C_{ss,av}$ | average steady-state concentration |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CTA | Clinical Trial Agreement |
| CYP | cytochrome P450 |
| DSMB | data safety monitoring board |
| ECG | electrocardiogram |
| eCRF | electronic case report form |

| Abbreviation | Term |
|---|---|
| ED | early discontinuation |
| ELISA | enzyme-linked immunosorbent assay |
| FAQ | Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire) |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FLAIR | fluid-attenuated inversion recovery |
| GCP | Good Clinical Practice |
| GDS | Geriatric Depression Scale |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |
| HCVAb | hepatitis C virus antibody |
| HSV | herpes simplex virus |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ID | identifier |
| IEC | Independent Ethics Committee |
| Ig | immunoglobulin (eg, IgA, IgG, IgM) |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISLT | International Shopping List Task |
| IxRS | interactive voice and web response system |
| LLN | lower limit of normal |
| LNH | low/normal/high |
| LP | lumbar puncture |
| MAD | multiple ascending dose |
| MCI | mild cognitive impairment |
| MCI/Prodromal | Mild Cognitive Impairment due to Alzheimer's Disease/ Prodromal Alzheimer's Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mild to moderate AD | mild to moderate dementia due to Alzheimer's Disease |
| miRNA | micro-ribonucleic acid |
| MMRM | mixed-effects model with repeated measures |
| MMSE | Mini-Mental State Examination |
| MRI | magnetic resonance imaging |

| Abbreviation | Term |
|---|---|
| NAT2 | N-acetyltransferase 2 |
| NIA-AA | National Institute on Aging-Alzheimer's Association |
| PBMC | peripheral blood mononuclear cell |
| PD | Pharmacodynamic(s) |
| PET | positron emission tomography |
| PGx | pharmacogenomic(s) |
| PK | pharmacokinetic(s) |
| PRN | Pro re nata |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| p-tau | phosphorylated-tau |
| QD | once daily |
| QTc | corrected QT interval |
| QTcF | QTc interval calculated using Fridericia's formula |
| R | randomization |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reaction |
| SUVR | standardized uptake value ratio |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |
| TEMAV | treatment-emergent markedly abnormal laboratory values |
| t-tau | total tau |
| ULN | upper limit of normal |
| UNS | unscheduled |
| vMRI | volumetric magnetic resonance imaging |
| WHO DD | World Health Organization Drug Dictionary |
| β-hCG | beta-human chorionic gonadotropin |

# 5 ETHICS

## 5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA][s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigators or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

## 5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (CFR) (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

- European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved European Union member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

## 5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject and the identified caregiver or informant, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or understand it or if the identified caregiver or informant is unable to read, an impartial witness should be present during the entire informed consent discussion. If, in the Investigator's opinion, a subject lacks capacity to consent, the subject's assent should be obtained in addition to the written informed consent of a legal representative (capacity to consent and definition of legal representative should be determined in accordance with applicable local laws and regulations). (revised per Amendment 01) After the ICF and any other written information to be provided to subjects is read and explained to the subject and the identified caregiver or informant, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified caregiver or informant should also consent to supporting the subject's participation in the study and will be provided with a separate written ICF for his or her participation in the study, to be signed before he or she participates in any further aspects of the study.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified caregiver or informant must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified caregiver or informant will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified caregiver or informant should be

informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

All subjects will also be asked to provide written consent for cerebrospinal fluid (CSF) sampling at Baseline and after receiving study drug for from 4 weeks and up to 18 months (or at Early Discontinuation). This consent for CSF sample collection is not required for study eligibility. (revised per Amendments 02 and 05)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects and will be via a separate, optional CSF consent form for the study. (revised per Amendment 04)

# 6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 35 investigational sites in the United States. (revised per Amendments 01, 02, 04, and 05)

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

# 7 INTRODUCTION

At this time, there is no cure for Alzheimer's disease (AD), no known way of slowing down the progression of this disease, and no approved treatment available to reverse the deterioration. There is, therefore, an urgent unmet medical need for drugs that slow or prevent disease progression. Beta-amyloid converting enzyme 1 (BACE1) is a key enzyme responsible for the production of amyloid β (Aβ) peptides and plaque formation, and several reports have described elevated levels of BACE1 in AD brains (Coulson, et al., 2010; Lu, et al., 2012). Once amyloid plaques form, Aβ causes BACE1 levels to increase further, thus accelerating Aβ generation and plaque growth via a positive feedback loop. Therefore, BACE1 is a promising target for modifying or treating AD.

It is now widely accepted that mild cognitive impairment (MCI) due to AD and mild to moderate AD dementia are stages on a single disease spectrum, which follows an Alzheimer's pathological cascade. (revised per Amendment 01) Recent consensus papers from the international workgroups of the National Institute on Aging-Alzheimer's Association (NIA-AA), have endorsed this hypothesis (Albert, et al., 2011; Jack, et al., 2011; McKhann, et al., 2011; Rosen, et al., 1984; Sperling, et al., 2011).

From a clinical standpoint, demonstration of an effect on slowing disease course is hampered by the lack of sensitive tools for detecting relatively small changes in progression or treatment effect especially in early disease. In addition, drugs that are expected to slow disease progression require longer study durations to ensure adequate separation from placebo. These challenges have resulted in the use of biomarkers as surrogates for clinical effect in Phase 2 studies, in order to facilitate the development process for disease modifying agents. However, subsequent Phase 3 AD studies based solely on biomarker findings in Phase 2 have failed to show clinical effect, due, in part, to the fact that biomarkers may not predict clinical outcomes for potential disease modifying agents. These findings underscore the need for innovative approaches to clinical study design for measuring the effect of treatment.

E2609 is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, E2609 inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in cerebrospinal fluid (CSF) and plasma (rat, guinea pig, and monkey). In humans, E2609 has been shown to inhibit BACE1 enzyme activity in CSF and lower the levels of Aβ, including amyloid beta monomer from amino acid 1 to x (Aβ[1-x]), Aβ(1-40) and Aβ(1-42), in CSF both in vitro and in vivo. See the Investigator's Brochure for additional information. The target indication for E2609 is therefore treatment and disease modification of AD.

The present clinical study is a Phase 2 study for the E2609 program, and is designed to establish safety in subjects with Mild Cognitive Impairment due to Alzheimer's Disease/Prodromal Alzheimer's Disease (referred to as MCI/Prodromal throughout the protocol) and in subjects with mild to moderate AD. (revised per Amendment 05) Results from this study will guide both the decision to move into Phase 3 development and the selection of the dose strengths to be taken into Phase 3.

In the MCI/Prodromal and mild to moderate AD population, this study will compare placebo and 3 oral doses of E2609 (5, 15, and 50 mg) administered once daily (QD) for 18 months. (revised per Amendment 05)

This study will include interim evaluations of the pharmacokinetic (PK), pharmacodynamic (PD), safety, and tolerability of chronic dosing with E2609. (revised per Amendment 05) Furthermore, there will be close monitoring of safety by an independent data safety monitoring board (DSMB), including a formal safety review as soon as the randomized subjects (n=60, ±20%) have completed at least 12 weeks of treatment, have discontinued study drug or have withdrawn from the study. (revised per Amendments 04 and 05) The study also includes a number of exclusion criteria, specific blinded safety monitoring procedures and safety criteria for discontinuation of study drug in light of the preclinical and clinical safety data collected to date following administration of E2609.

## 7.1 Results of Interim Evaluations

(revised per Amendment 06)

Unblinded interim evaluations of the safety and tolerability of E2609 suggested favorable safety at all doses of E2609. Additionally, analyses of the PD effects (reduction from baseline in CSF Aβ levels) of E2609 5, 15, and 50 mg per day have indicated that E2609 50 mg per day produced relatively high levels of CSF Aβ reduction (greater than 50%). Based on the results of these analyses, E2609 50 mg per day has been selected as the dose for Phase 3 development.

As E2609 5 and 15 mg per day will not be advanced clinically, subjects initially randomized to the E2609 5 and 15 mg per day treatment arms will be re-assigned in a blinded manner to the E2609 50 mg treatment arm provided that they will have at least 12 weeks of treatment remaining in the Randomization Phase. The purpose of this dose re-assignment is to further characterize the safety and tolerability of E2609 50 mg.

## 7.2 Nonclinical and Clinical Safety Data

The toxicity of E2609 has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomologus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by E2609 in a clinical setting. Further details of the nonclinical data to date with E2609 can be found in the Investigator's Brochure.

The clinical program to date includes 6 Phase 1 studies:

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, single ascending dose (SAD) study that investigated doses ranging from 5 to 800 mg in

healthy adult subjects (aged 30 to 55 years) and elderly subjects (50-mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled MAD study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of E2609 and the PD effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of E2609. It also investigated the effects of E2609 on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [$^{14}$C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of E2609 under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) was a randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with E2609. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with E2609. In elderly subjects treated with 50 mg of E2609, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTc interval calculated using Fridericia's formula (QTcF) from baseline (14.9 msec at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of E2609 might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that E2609 altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of E2609. A single dose of E2609 up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, E2609 administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of E2609 on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP3A4] and carboxyesterase-2 [CES2]) increased by approximately 70% the area under the concentration × time curve (AUC) of E2609. Consequently, strong inhibitors of CY3A4 will be prohibited in this study.

Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of E2609. Therefore, no restrictions are required for the use of concomitant medications which are known to be inducers of CYP450 enzymes. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of E2609 when coadministered with E2609 but not when dosed at least 2 hours apart from E2609. E2609 (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of E2609. Therefore, on the basis of drug interaction considerations, the only restriction of concomitant medications is that for strong inhibitors of CYP3A4.

# 8 STUDY OBJECTIVES

## 8.1 Primary Objective

(revised per Amendment 05)

The primary objective is:

- To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with mild to moderate AD (revised per Amendment 01)

## 8.2 Secondary Objectives

The secondary objectives are: (revised per Amendments 02 and 05)

- To characterize the plasma and CSF PK of E2609
- To assess the effects of E2609 on Aβ(1-x) and Aβ(1-42) in CSF from 4 weeks and at 18 months of treatment

## 8.3 Exploratory Objectives

(revised per Amendments 01,02, 04, and 05)

The exploratory objectives are:

- To explore the effects of E2609 compared on CSF Aβ(1-40) and BACE1 measurements from 4 weeks and up to 18 months of treatment
- To explore the effects of E2609 compared with placebo on various biomarkers. Biomarkers to be explored may include, but not limited to:
  a. CSF biomarkers of neurodegeneration (eg, total tau [t-tau], phosphorylated-tau [p-tau]) after 18 months of treatment
  b. Plasma and CSF amyloid, and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment (revised per Amendment 06)
  c. Total hippocampal atrophy at 12 and 18 months of treatment, as measured by volumetric magnetic resonance imaging (vMRI)
  d. vMRI measurements including left and right hippocampal volume, whole brain volume, and total ventricular volume at 6, 12, and 18 months of treatment
  e. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)

- To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during posttreatment follow-up by assessment of:
  a. The Alzheimer's Disease Assessment Scale – cognitive subscale ($ADAS\text{-}cog_{14}$)

b. The Clinical Dementia Rating (CDR) scale
c. The Mini-Mental State Examination (MMSE)
d. The International Shopping List Task (ISLT)
e. The CogState Brief Battery (CBB)
f. The Functional Assessment Questionnaire (FAQ; (also known as the Functional Activities Questionnaire)

- To explore the relationship between the treatment effects of E2609 on measured clinical efficacy scales (eg, MMSE, CDR) and its effects on CSF amyloid, CSF amyloid isoforms, brain amyloid, and vMRI
- To explore relationships between both E2609 dose and exposure, with PD and safety endpoints

# 9 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan

This study is a multicenter, placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild to moderate AD. (revised per Amendment 01)

A common set of inclusion criteria, consistent with the NIA-AA clinical research criteria for MCI due to AD or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study consists of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days, plus an additional window of up to 30 days if required [revised per Amendment 02]) will consist of a Screening Visit and a Baseline Visit. Screening assessments will be organized into 4 tiers; see Section 9.5.2.2, Table 6, and Figure 2.

All screening assessments must be completed, and eligibility to continue to the Baseline Period confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

All subjects (MCI/Prodromal and mild to moderate AD) will initially be randomized 1:1:1:1 to 4 treatment groups (5, 15, or 50 mg E2609 or placebo) (revised per Amendments 01 and 05). Upon implementation of Amendment 06, at the next regularly scheduled visit, subjects receiving E2609 5 or 15 mg who have not yet completed Visit 17 (Week 66), will be re-assigned in a blinded manner to E2609 50 mg for the remainder of the treatment period. In order to maintain the blind, all subjects who have not yet had Visit 17 will go through the same procedures with the placebo-randomized subjects continuing to receive placebo and those randomized to E2609 50 mg continuing to receive 50 mg. (revised per Amendment 06)

An overview of the study design is presented in Figure 1.

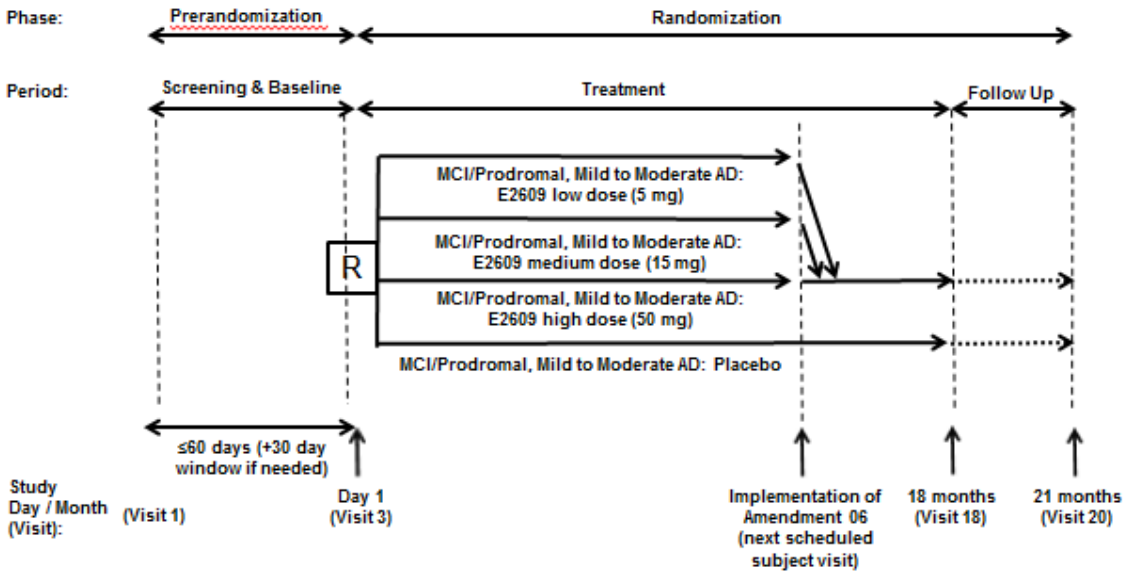



**Figure 1 Design of Study E2609-G000-202**

**(revised per Amendments 01, 02, 05, and 06)**

R = randomization, AD = Alzheimer's Disease, MCI = mild cognitive impairment.

This study will be limited to approximately 35 sites in the United States, with approximately 60 (±20%) eligible subjects randomized at Visit 3, 1:1:1:1 to 4 treatment groups within each clinical cohort. In addition to the placebo group, 3 doses of E2609 will be used to reduce CSF Aβ levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/PD modeling shows these doses should achieve these targets when administered QD with food and will be evaluated based on the 4-week (or later) assessment of CSF Aβ(1-x) from subjects who provide voluntary consent for CSF measurement (see Section 9.4.4 ). (revised per Amendments 01, 02, 04, and 05) Safety data will be monitored in a blinded fashion on a regular basis.

In addition, approximately every 3 months from the time the 1st subject is randomized into the study through the time the last subject is randomized, an independent DSMB (including at least 1 immunologist) will review all safety data in an unblinded manner. (revised per amendment 06) The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. (revised per Amendments 01, 04, and 05)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

Interim analyses of the E2609 plasma PK for all subjects and the E2609 CSF PK and PD profiles will be performed on baseline data and samples collected after at least 4 weeks of

treatment. (revised per Amendment 05) Refer Section 9.7.3 for more detail. These data will be used to evaluate the CSF PD effects of E2609 doses, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels (see Section 9.4.4). The median and mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks or more of treatment for each dose of E2609 and the 90% confidence interval (CI) for the median will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline determined after at least 4 weeks of dosing. (revised per Amendments 01, 02, 03, and 04)

Once subjects have completed at least 12 weeks of treatment (or discontinued study drug early), an interim safety analysis will be conducted by Eisai and the DSMB. (revised per Amendments 01, 04, and 05) At the completion of this interim safety review, the frequency of subsequent unblinded safety reviews will be re-evaluated by the DSMB and the Sponsor and this information will be provided in the DSMB charter. (revised per Amendment 06) Subjects will continue study drug while the DSMB reviews all the available safety data. (revised per Amendment 05) At the time of this interim safety analysis, some subjects will have more than 12 weeks of safety data.

Interim analyses are planned and are discussed in Section 9.7.3. (revised per Amendment 03)

Based on the results of the interim analyses, the E2609 50 mg dose has been chosen as the clinical dose for the Phase 3 studies. In order to collect additional safety data for E2609 50 mg, subjects randomized to E2609 5 or 15 mg in this study will be re-assigned to E2609 50 mg if and only if these subjects have at least 12 weeks of treatment remaining in the Randomization Phase following study drug dose re-assignment. Therefore, subjects who completed Visit 17 assessments prior to the implementation of Amendment 06 will remain on their original randomized dose. As study drug dose re-assignment will occur in a blinded manner, a 4-week interim safety assessment following study drug re-assignment will be required for all subjects. (revised per Amendment 06)

### 9.1.1 Prerandomization Phase

The Prerandomization Phase includes a Screening Visit and a Baseline Visit. All Screening Visit assessments must be completed and eligibility to progress must be confirmed before any Baseline Visit assessments are performed. All Screening Visit and Baseline Visit assessments must be completed within 50 days (plus an additional window of up to 30 days if required [revised per Amendment 02]) and a window of no more than 10 days is to be observed between the completion of all Baseline Visit assessments (including confirmation of eligibility following all Baseline Visit assessments) and randomization into the study at Visit 3 (revised per Amendment 02). Thus, the Prerandomization Phase will last for up to 60 days, plus an additional window of 30 days if required (revised per Amendment 02). The series of assessments conducted during this phase will determine eligibility for randomization into the study.

Inclusion criteria are discussed in Section 9.1 and detailed in Section 9.3.1. Before randomization, the clinician will provide a judgment on the classification of a subject as either MCI/Prodromal or likely mild to moderate AD. (revised per Amendment 01) This judgment may be discussed and reviewed with the Sponsor or Sponsor's representative, as necessary.

Results of the Screening safety magnetic resonance imaging (MRI) will be valid for 90 days from the date of scanning. Results of the lumbar puncture (LP) from subjects who voluntarily consent for CSF measurement will be valid for 90 days from the date of testing. Results of Screening PET scans conducted specifically for this study and for use in the longitudinal analyses will also be valid for 90 days from the date of scanning. These assessments will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. Historical PET scans used for determination of eligibility only (ie, not used for the longitudinal analyses) are valid for 12 months. (revised per Amendment 02)

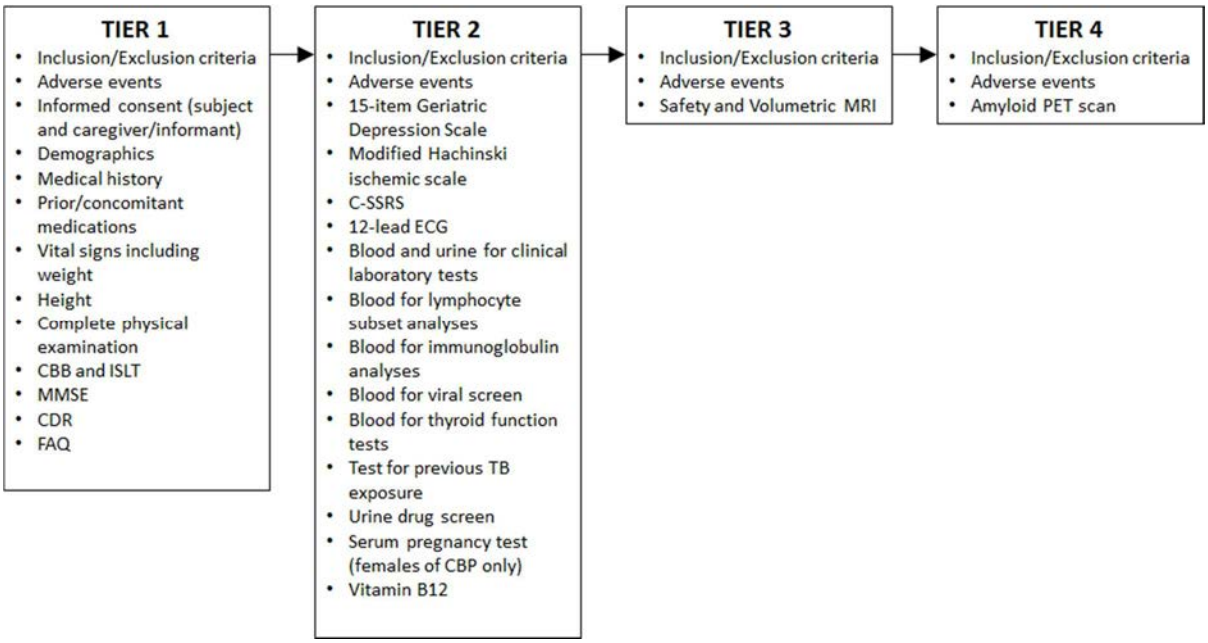
#### 9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and caregiver or informant, and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained from both the subject and the caregiver or informant. The caregiver or informant needs to be present at this visit.

Study site personnel will interview the subject and caregiver or informant to obtain demographic and clinical information as described in Table 6, and will review inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2 and perform any required assessments in order to complete these criteria. Prior medications and medications currently being taken by the subject will be reviewed (see Section 9.4.7). The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

Clinical assessments for eligibility will be conducted during the Screening Visit as described in Table 6 and Figure 2.

Every effort should be made to conduct these assessments in the morning, but if this is not possible, they should be conducted at the same time of day at all subsequent visits. The screening assessments/procedures have been organized into 4 distinct tiers (Table 6 and Figure 2). All assessments/procedures in each tier should be completed, and eligibility to continue screening in the study confirmed, before any assessments/procedures from the next tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures as long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. (revised per Amendment 01)




## Figure 2 Assessments to be Performed at Screening by Tier

CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), ISLT = International Shopping List Task (immediate and delayed recall), MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PET = positron emission tomography, TB = tuberculosis.

Cognitive assessments (Tier 1) are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). The recommended order of assessments at Screening is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. (revised per Amendment 02) The investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session (Tier 3).

Amyloid PET imaging will be used to confirm all subjects have amyloid deposition in the brain (Tier 4). An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. If an historical amyloid positive PET scan is being used, it should be submitted to the central PET reading group after the subject has completed and passed all Tier 1 assessments (revised per Amendment 02)

#### 9.1.1.2 Baseline Period

All Screening Visit assessments must be completed (and eligibility to progress confirmed) before any Baseline Visit assessments are performed. The Baseline Visit assessments (per Table 6 and Section 9.5.1.2) are to be completed as soon as possible after completion of the final Screening Visit assessment (ie, PET scan) such that all Screening Visit and Baseline Visit assessments are completed within 50 days, plus an additional window of up to 30 days if required. (revised per Amendment 02)

Inclusion and exclusion criteria will again be reviewed, vital signs including weight will be recorded, and a 12-lead ECG will be conducted in triplicate. A routine physical examination will be conducted and a dermatological assessment and neurological examination (including the Brief Smell Identification Test [Sensonics Inc.]) will be performed. (revised per Amendment 04) A urine pregnancy test will be conducted for females of childbearing potential. Blood will be collected from all subjects for clinical chemistry and hematology, lymphocyte subset analyses, Ig analyses, and PD assessments. Blood samples will be collected and stored for determination of a subject's previous exposure to infective pathogens in the event of AEs that warrant further investigation occurring at a later point in the study. Psychometric assessments will be administered to the subject in the order stated in Table 6. The caregiver or informant needs to be present at this visit. The Columbia Suicide Severity Rating Scale (C-SSRS) will also be administered (Section 9.5.1.5.11).

For subjects who consent to CSF sample collection, a CSF sample will be obtained at this visit for PK and PD assessments (see Section 9.5.1.4). (revised per Amendment 02)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

Blood will be collected from all subjects for pharmacogenomic (PGx) analyses of apolipoprotein E (*ApoE*) and the N-acetyltransferase 2 (*NAT2)* phenotype of subjects enrolled in the study (see Section 9.7.1.7.2).

### 9.1.2 Randomization Phase

Subjects who complete the Baseline Visit assessments, and are eligible based on the inclusion and exclusion criteria (see Section 9.3.1 and Section 9.3.2), will begin the Randomization Phase no more than 10 days after completion of the Baseline Visit assessments and confirmation of the eligibility of the subject based on the results of all the Baseline Visit assessments (revised per Amendment 02).

The Randomization Phase will consist of a Treatment Period of 78 weeks duration and a Follow-Up Period of 12 weeks after the last dose of study drug.

#### 9.1.2.1 Treatment Period

Subjects will be randomized at the beginning of the Treatment Period and will receive study drug or placebo, to be administered orally QD with food. Double-blinding to study drugs will be in effect throughout the Treatment Period. (revised per Amendment 06)

Safety criteria for discontinuation of study drug are detailed in Section 9.3.3.

Subjects will attend the study site every week for the first 4 weeks after beginning study drug, then fortnightly until 12 weeks have elapsed since first dose. Visits will then be conducted at 16, 20, 26, 39, 52, 65, and 78 weeks after the first dose.

#### 9.1.2.2 Early Discontinuation

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug. (revised per Amendments 04 and 05)

#### 9.1.2.3 Follow-Up Period

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 4 posttreatment Follow-Up Visits: 2, 4, 8, and 12 weeks after the last dose of study drug. If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the post-treatment Follow-Up Period. (revised per Amendment 04)

The end of the study will be defined as the date of the clinical database lock (ie, when all study data are collected and data validation is completed).

As required by some regulatory agencies, the following estimates are provided:

- The study will begin in Nov 2014 and is projected to end by Apr 2018. (revised per Amendment 05)
- The maximum estimated period for each subject on study is anticipated to be approximately 2 years.

## 9.2 Discussion of Study Design, Including Choice of Control Groups

### 9.2.1 Overview

The primary objective of the study is to assess the safety and tolerability of daily dosing with E2609 in subjects with MCI/Prodromal AD and in subjects with mild to moderate AD. Immunological and hematological parameters will also be assessed. (revised per Amendment 04)

The inclusion criteria for the MCI/Prodromal cohort will be consistent with the NIA-AA criteria for MCI due to AD (Albert, et al., 2011) and with the definition of Prodromal AD per Dubois et al., 2010 (see Section 9.2.2).

There is no active or positive control for this study as at this time, there is no cure for AD, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

Secondary endpoints include CSF PK and plasma PK parameters of E2609 based on population PK analysis and the percentage reduction of Aβ(1-x) and Aβ(1-42) in CSF relative to baseline from 4 weeks and up to 18 months of treatment. The intrinsic and extrinsic factors on the PK characteristics will also be explored.

Exploratory endpoints include CSF Aβ(1-40) and BACE1 measures as well as CSF biomarkers of neuronal degeneration (eg, t-tau and p-tau), volumetric MRI measurements, plasma amyloid measurements, brain amyloid levels as measured by amyloid PET and clinical assessments. (revised per Amendment 05) Exploratory endpoints including assessments of efficacy, safety, and other biomarkers are also included.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups (Section 9.7.4) Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

The rationale for the selection of doses used in the study is provided in Section 9.4.4.

### 9.2.2 Rationale for Study Population

By the time AD progresses to dementia, with loss of functional capabilities, the amyloid load in the brain is approaching a plateau and significant neurodegeneration has occurred (Jack, et al., 2010). Consequently, there is a growing view within the AD field that it may be necessary to initiate disease modifying treatments earlier, before the onset of clinical dementia (Aisen, et al., 2010). However, this hypothesis remains to be demonstrated with clinically effective therapies, and may not apply to all therapeutic classes, it is possible that this consideration explains the failure of the humanized monoclonal antibody bapineuzumab (which targeted brain amyloid) to demonstrate clinical efficacy in late-phase studies in mild to moderate AD dementia. (revised per Amendment 01)

With this consideration taken into account, the primary clinical population of focus in this study is subjects with MCI/Prodromal AD. The mechanism of action of a BACE1 inhibitor where amyloid production is reduced means E2609 is more likely to be efficacious (ie, slow disease progression) the earlier in disease progression treatment is started, where limited neurodegeneration has occurred and associated clinical deficits are at a minimum. However, since the effect of BACE1 inhibition along the AD continuum remains to be characterized, E2609 will also be evaluated for its profile in mild to moderate stages of AD, in the event

data emerge supporting its use beyond MCI/Prodromal AD. Indeed, recent data support the notion of continued progression of amyloid pathology even in these later stages of the disease (Hu, et al., 2015), although at a slower pace, suggesting a positive effect of BACE inhibition and amyloid beta reduction cannot be ruled out even in the later stages of the disease trajectory. Hence, in this study, E2609 will be assessed in subjects with disease states ranging from MCI/Prodromal to mild and even moderate AD. (revised per Amendment 01)

As discussed, efficacy is more likely to be observed in subjects with MCI/Prodromal AD but there is the possibility that efficacy will also be evident following administration of an amyloid modifying agents such as E2609 in subjects with more advanced disease such as mild to moderate AD. (revised per Amendment 01) For example, a study of tarenflurbil, a selective Aβ(1-42)-lowering agent, on cognition and function in subjects with mild to moderate AD showed the subjects with mild AD had lower rates of decline than those in the placebo group in activities of daily living and global function; however, slowing of cognitive decline did not differ significantly (Wilcock, et al., 2008). Similarly, differential effects on cognitive measures have been observed with solanezumab, where some benefit from treatment was observed in subjects with mild AD, although studies with solanezumab were considered to have failed to improve cognition or functional ability significantly (Doody, et al., 2014). Therefore, it is relevant to compare the effect of the BACE1 inhibitor E2609 in 2 different subject populations that differ in terms of AD severity before the initiation of large Phase 3 clinical studies. (revised per Amendment 01)

### 9.2.3 Rationale for Clinical Endpoints

The 14-item version of the ADAS-Cog will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007).

The CDR is a clinical global rating scale requiring the interviewing of both the subject and an informant who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975)

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al,. 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials on the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson et al., 2011, Lim, et al., 2012a, Lim, et al., 2012b). Data computations indicate

that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with E2609 treatment.

The CBB is a brief, computer-administered cognitive test battery that requires approximately 10 minutes for administration (Darby, et al., 2012; Fredrickson, et al., 2008; Maruff, et al., 2009). The CBB has been used to detect cognitive impairment in several neurodegenerative conditions including the measurement of cognitive function in healthy older adults and in adults with clinically diagnosed AD and prodromal AD (Darby, et al., 2009; Hammers, et al., 2012; Lim, et al., 2012a; Lim, et al., 2012b). The administration, scoring, and reporting of the CBB is automated and highly standardized, resulting in cognitive paradigms that have been well-validated in neuropsychological and cognitive studies (Fredrickson, et al., 2008; Maruff, et al., 2009). See Section 9.5.1.3.1 for further details.

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression. Volumetric magnetic resonance imaging is discussed in Section 9.2.4.4.

## 9.2.4 Rationale for Biomarkers

### 9.2.4.1 Overall Rationale

The biomarker strategy for this study includes the following aims:

- To establish an amyloid load in the brain at study entry (via the PET eligibility inclusion criterion)
- To evaluate safety (principally by MRI)
- To evaluate a PD effect in terms of both Aβ in CSF and brain amyloid assessed by amyloid PET and to establish that this PD effect is maintained long-term (revised per Amendment 02)
- To evaluate disease modification through longitudinal assessments of vMRI, amyloid PET, and CSF biomarkers of neurodegeneration (t-tau and p-tau)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

### 9.2.4.2 Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect of E2609 on Aβ(1-40) +Aβ(1-42) and other C-terminally truncated Aβ peptides such as Aβ(1-38) through inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using [$^{11}$C]PiB, suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain

parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases in CSF Aβ concentrations that are seen in AD are believed to be related to this decrease in brain Aβ availability.

Both t-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni and Bhaskar, 2012). CSF tau measurements have been correlated with cerebral atrophy, while their ratios with Aβ42 have provided useful predictors of cognitive decline and progression to dementia due to AD. Rebalancing dysregulated amyloid production early in the process may positively affect the neurodegenerative process and thus affect these markers and benefit the disease trajectory. Therefore, monitoring these markers in conjunction with amyloid imaging may provide further supportive evidence of disease modifying effects. (revised per Amendment 04)

Baseline levels of Aβ(1-42), t-tau, and p-tau will also help elucidate the extent of AD pathology at entry to the study and can be combined with baseline levels of *ApoE4* genotyping in addition to the baseline imaging variables to help explain differences in treatment response.

The study will be stratified at randomization for *ApoE4* gene status in order to account for any *ApoE* status by treatment interaction or *ApoE* status by amyloid-related imaging abnormalities risk interaction.

#### 9.2.4.3 Amyloid PET

Amyloid PET imaging will be used in this study for 2 primary reasons: 1) to confirm the presence of AD pathology in the brain of subjects with MCI/Prodromal AD or mild to moderate AD at entry to the study; and 2) to evaluate the effects of E2609 on amyloid levels in the brain, both by whole brain analysis (the average of 5 to 6 cortical regions) and brain region analysis. (revised per Amendment 01)

Longitudinal amyloid PET imaging will be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug) as an exploratory measure of the potential disease-modifying effects of E2609. Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses). (Revised per Amendments 02 and 05)

#### 9.2.4.4 vMRI

Volumetric imaging will be used to evaluate the effects of E2609 on rates of atrophy across the different dose groups and to provide support that effective treatment is associated with modification of disease course (secondary endpoint for the MCI/Prodromal population and exploratory endpoint for the mild to moderate AD population). (revised per Amendment 01) A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the

brain (frontal cortex) in its later stages. Clinically efficacious doses are predicted to be associated with a slowing in the rate of hippocampal atrophy compared with rates observed in the placebo and non-efficacious dose groups. Treatment effects on left and right hippocampal, whole brain, and total ventricular volumes are exploratory endpoints.

Annualized rates of change of 2% to 3% have been reported for the AD brain compared with 1% in MCI and <1% in age-matched controls (Hua, et al., 2010, Leung, et al., 2010). However, subjects with MCI due to AD-dementia (CSF Aβ <192 pg/ml or positive amyloid imaging) show rates of atrophy comparable to those observed in subjects with AD-dementia (Hua, et al., 2009; Hua, et al., 2010; Leung, et al., 2010; Morra, et al., 2009), supporting the notion that such subjects are on similar trajectories as those with mild AD-dementia. Lower levels of CSF Aβ42, amyloid positivity on PET imaging, and higher levels of CSF t-tau in addition to the presence of the *ApoE4* allele have all been associated with greater rates of brain atrophy (Fjell, et al., 2010a; Fjell, et al., 2010b) and will be entered as covariates in various analyses. Hippocampal atrophy has also been shown to predict clinical progression independently of amyloid levels in the brain (Jack, et al., 2010), and this measure will be entered as a covariate in the analysis of the clinical endpoints along with the aforementioned variables.

Brain volume (total ventricular volume, whole brain, temporal lobe) generally shows a modest correlation with performance on a number of cognitive scales (Hua, et al., 2009; Hua, et al., 2010; Freeborough, et al., 1997; Leung, et al., 2010). Using volumetric analysis performed at 6-month intervals, these relationships and the effects of E2609 treatment will be explored further. Recent advances in analysis software have made structural imaging more sensitive to detect small changes and able to reliably measure rates of atrophy at these intervals, particularly in the posterior parietal and the lateral temporal regions during the early stages of disease (Hua, et al., 2009; Hua, et al., 2010). Given these observations, a demonstration of significant slowing or stabilization in the rate of atrophy in response to treatment, compared with placebo, will offer further support for disease modification.

### 9.2.5 Clinical Risks and Mitigation Strategy

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, and to mitigate clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. These safety aspects include the following:

- Immunology-related and infection-related exclusion criteria
- Review of unblinded safety data by an independent DSMB at regular intervals
- Safety criteria for discontinuation of study drug based on CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cell) and other lymphocytes (absolute counts and percentage change from baseline), skin rash, reoccurrence of herpes virus infections including any oral herpes, genital herpes or shingles, other infections, MRI changes, ECGs, and pregnancy.

In addition to the features above, other safety aspects of this study designed to mitigate clinical risk include the following:

- Blinded safety data will be monitored by Eisai at regular intervals during the course of the study
- Routine safety assessments will include the monitoring and recording of all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events. To assess potential immunomodulatory effects, peripheral blood mononuclear cells (PBMCs) will be collected at baseline, during treatment, and post-treatment.

As per the communication from the Food and Drug Administration (FDA) in Aug 2013, there are concerns that hypopigmentation of the skin and mucous membranes may occur with BACE1 inhibitory drugs. Although no such effects have been seen with E2609 to date, assessments by a reviewing dermatologist will be performed at regular intervals during the study. These assessments will be made centrally, using standardized photography and will

specifically include evaluation of any areas of depigmentation or any rash. Dermatological assessments will be supplemented with a specific question to subjects regarding skin changes at each visit. Any such changes could be referred to the central reviewing dermatologist, and to a local dermatologist if needed, for further evaluation. See Section 9.5.1.5.8 for further details.

- Baseline and on-study blood and DNA samples will be taken and stored for all subjects, and CSF samples will be taken and stored for all subjects who consent to CSF sample collection (revised per Amendment 02). These samples may be tested in the event that a subject develops AEs that warrant further investigation (eg, if a subject develops a treatment-emergent infection) (see Section 9.5.1.2.2).
- Central reading of safety brain MRI assessments (including any MRI evidence of demyelination) will be performed at Screening, at approximately 6-month intervals during the Treatment Period, and at the final Follow-Up Visit.
- Full neurologic examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. Details of the neurologic examination are given in Section 9.5.1.5.9.
- Cognitive decline will be assessed as a safety assessment (ADAS-cog$_{14}$, MMSE, and CBB). Of particular importance will be the assessment of reaction time testing using the detection and identification tasks on the CBB.
- An assessment of suicidality using the C-SSRS will be performed at Screening, Baseline, and at regular intervals during the Treatment and Follow-Up Period (see Section 9.5.1.5.11).
- All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will have at least 4 off-treatment Follow-Up visits (2, 4, 8, and 12 weeks after the last dose of study drug). More frequent safety assessments can be made as unscheduled assessments/visits during the off-treatment Follow-Up period, if clinically indicated. (revised per Amendment 04)
- An ophthalmic examination will be conducted at Baseline and if the subject experiences visual disturbances during the course of the study (see Section 9.5.1.2.1).

## 9.3 Selection of Study Population

Approximately 60 (±20%) eligible MCI/Prodromal or mild to moderate AD subjects will be randomized at approximately 35 sites in the United States (revised per Amendments 02 and 04). There will be no restriction to the number of subjects from either population.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

### 9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD (Albert, et al.,

2011) or AD dementia (McKhann, et al., 2011) and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at Screening Visit 1:**

(revised per Amendment 02)

a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation

b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT. Alternatively, cognitive impairment of at least 0.5 SD from age-adjusted norms in delayed recall on the ISLT plus impairment of at least 1 SD from age-adjusted norms in at least 1 other computerized learning and memory test (ISLT immediate recall, or 1 of the learning and memory components of the CBB). (revised per Amendment 02)

c. FAQ ≤24 (revised per Amendment 01)

d. MMSE ≥16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading; an historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group (revised per Amendment 02)

3. Male or female, age 50 to 85 years, inclusive at time of consent

4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.

5. If receiving acetylcholinesterase inhibitors (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the Baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.

6. Must have been on stable doses of all other permitted chronically used concomitant

medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization

### 9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or MRI
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and <1cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could, in the opinion of the investigator, confound the MCI/Prodromal or mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendments 01 and 02)
7. A score of ≥8 on the 15-item Geriatric Depression Scale (GDS) at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the LLN for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices

other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.

12. Any contraindications to LP for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity). Only applicable to subjects consenting to CSF sample collection (revised per Amendment 02)
13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of Ig deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization.
20. Any active infection within the last 4 weeks prior to randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below population-adjusted LLN at Screening or Baseline and confirmed by a repeat test conducted 1 week after the initial test. The population-adjusted LLN for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are 396, 157, and 74 cells/μL respectively. See Appendix 5. (revised per Amendment 02)
23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the Investigator and the Medical Monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of clinical immunodeficiency. The discussion with the Medical Monitor should include a

detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)

24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate ECGs. A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute (bpm) at Screening or Baseline
29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.
33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo). Diagnosis of an underlying disease causing hypopigmentation is not necessary for exclusion if the clinical presentation is consistent with such a condition. Hypopigmentation associated with scarring need not be exclusionary. (revised per Amendment 02)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the C-SSRS suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before

Screening

37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period or for 28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.
    - Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
    - (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]). (revised per Amendment 04)

### 9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may discontinue study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to stop study drug or withdraw from the study at any time for any reason.

Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). Follow-Up Visits will also be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug (see Section 9.1.2.3). (revised per Amendments 04 and 05)

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the Subject Disposition eCRF page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study drug and withdraws from the study at the same time, the ED Visit will be followed (see Section 9.5.5).

Safety-related criteria for discontinuation of study drug include the following:

a. A study drug discontinuation threshold will be set based on absolute counts of CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells). The discontinuation threshold will be set at below the level of the population-adjusted LLN (CD4=396 cells/µL; CD8=157 cells/µL; and CD19=74 cells/µL), at a level that represents a greater risk of opportunistic infection in the treated population. (revised per Amendment 02) For CD4 (T helper cells) the discontinuation threshold is 250 cells/µL. For CD8 (cytotoxic T cells) and CD19 (B cells) the discontinuation thresholds are 150 cells/µL and 50 cells/µL, respectively. Any subject who has CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below the discontinuation threshold as confirmed by a repeat test conducted within 1 week of the initial test but who has no clinical signs or symptoms of infection, will have study drug temporarily suspended for at least 2 weeks but no more than 4 weeks. During this period of study drug suspension, lymphocyte subset counts and complete blood count (CBC) with differentials will continue to be tested weekly until CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) have all returned to greater than the population-adjusted LLN after which time study drug can be resumed. Testing of lymphocyte subset counts and CBC with differentials is required weekly for 4 weeks following resumption of study drug administration. Temporary suspension and rechallenge with study drug is only permitted once for any given subject. If the lymphocytes and CD counts do not return to greater than the population-adjusted LLN within 4 weeks from the start of temporary suspension the subject will need to be permanently discontinued from study drug. (revised per Amendment 04)

b. Subjects with CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between the population-adjusted LLN and the discontinuation threshold will have lymphocyte subset counts performed on a weekly basis. (revised per Amendments 02 and 04) During the early stages of the treatment period, where visits are conducted weekly (ie, Visits 4, 5, 6, and 7), lymphocyte subsets are already scheduled to be

measured on a weekly basis and so additional visits or blood draws are not required. (revised per Amendment 02) For these subjects, the decision as to whether the subject remains on study drug or is to be discontinued from study drug will be based upon clinical judgment and will take into account any clinical presentation in addition to the lymphocyte subset counts. These subjects may continue with treatment if there is no clinical evidence of infection. They will be discontinued from study drug if they have infections of a moderate to severe intensity (eg, subjects whose infections are not localized, or are systemically unwell, or who require systemic anti-infective drug treatment).

**Table 1 Study Drug Actions for Lymphocyte Subset Absolute Counts**

| Lymphocyte subset absolute counts | Action | Decision to continue, discontinue, or temporarily suspend study drug |
|---|---|---|
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold and no clinical signs or symptoms of infection | Retest within 1 week along with<br>CBC with differentials | If retest performed within 1 week confirms lymphocyte subset counts below the discontinuation threshold, temporarily suspend study drug for between 2 and 4 weeks. Continue weekly testing of lymphocyte subsets and CBC with differentials. Rechallenge with study drug allowed when CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts all greater than population-adjusted LLN. Temporary suspension and rechallenge permitted only once for each subject. |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between population-adjusted LLN and discontinuation threshold | Lymphocyte subset counts (and CBC with differentials) to be performed weekly until lymphocyte subset counts return to ≥ population-adjusted LLN | Decision will be based upon lymphocyte subset counts and clinical judgment |

LLN = lower limit of normal, CBC = complete blood count.

(Table revised per Amendments 02 and 04)

c. Subjects with clinical evidence of infection will have their CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts measured. Blood and other biological samples will also be collected for investigations of infective pathogens (eg, serological tests, quantitative polymerase chain reaction, microscopy, and culture) where appropriate. In subjects with infection, if any of their absolute cell counts meets the discontinuation thresholds, study drug will be discontinued. All subjects with severe infections will be discontinued from study drug. All subjects with herpes zoster

(shingles) or ocular herpes infections will be discontinued from study drug, regardless of severity of presentation. Subjects with mild or moderate infection may continue treatment with study drug unless otherwise clinically indicated or otherwise specified below. Specifically, when any of the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are between the population-adjusted LLN and the discontinuation thresholds, subjects with infections of moderate intensity will be discontinued from study drug (eg, subjects whose infections are not localized, or subjects who are systemically unwell, or who require systemic anti-infective drug treatment). All subjects with infection who are discontinued from study drug will be followed for a period of 12 weeks or until the infection resolves/ stabilizes or until the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts have returned to greater than population-adjusted LLN (whichever comes latest). (revised per Amendments 02 and 04)

**Table 2 Study Drug Actions for Lymphocyte Subset Absolute Counts and Infection**

| Criterion | Severity of Infection | | | |
|---|---|---|---|---|
| | None | Mild | Moderate | Severe |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold | If confirmed with repeat testing within 1 week, then temporarily suspend study drug as per instructions above. | Discontinue study drug | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between population-adjusted LLN and discontinuation threshold | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts always > population-adjusted LLN | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated (See (e) for exception) | Discontinue study drug |

LLN = lower limit of normal.

(Table revised per Amendments 02 and 04)

d. A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (see (e) for exception), will be discontinued from study drug and a dermatological consult will be requested regardless of whether the rash is considered drug-related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study

drug, a dermatological consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

e. Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

f. Development of any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. If discontinued from study drug, subjects will undergo an ED Visit within 7 days after discontinuation and will attend the Follow-Up Visits 2, 4, 8, and 12 weeks after the last dose of study drug. They will also undertake an Unscheduled Visit (with MRI) at approximately 4 weeks after the visit at which such MRI features were first identified. An MRI will also be performed at approximately the time of the final Follow-Up Visit (Visit 20). Additional visits for safety may be arranged if clinically indicated in the opinion of the investigator, including after 12 weeks after the last dose of study drug. At any time during the treatment period, subjects who have asymptomatic, treatment-emergent microhemorrhages as detected by MRI, but none of the features which merit discontinuation of treatment (ie, vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic treatment-emergent microhemorrhage) may continue with treatment. These subjects will have safety assessments (including MRI) at approximately 4 weeks after the visit at which such MRI features were found. They will also continue with the scheduled MRI scans. Additional unscheduled MRI scans may be arranged on an individual subject basis in discussion with the study medical monitor. (revised per Amendment 04)

g. A postdose ECG with an average QTcF interval >500 msec from triplicate ECGs

h. A postdose ECG with a QTcF interval increase from baseline >60 msec and a QTcF interval >450 msec as demonstrated from triplicate ECGs

i. Any seizure (motor or non-motor)

j. Pregnancy

## 9.4 Treatments

### 9.4.1 Treatments Administered

For this study the test drug is E2609 and the control drug is placebo. All study drugs are to be administered orally, QD, with food.

Treatments to be administered are 5, 15, and 50 mg E2609 or placebo prior to the implementation of Amendment 06, and 50 mg E2609 or placebo after the implementation of Amendment 06 as shown in Figure 1. (revised per Amendments 01, 05, and 06) Study treatment will begin on Day 1 (at the study site) following Randomization and will continue for approximately 78 weeks. Please refer to Table 7 and Section 9.5.1.4.1 for specific information on drug administration on days when PK sampling is to be performed.

Study drug doses will remain the same for each individual subject unless the interim PK/PD analysis determines that an entire dose level requires adjustment (Section 9.4.4). See Section 9.3.3 for safety-related discontinuation criteria of study drug. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

### 9.4.2 Identity of Investigational Product

E2609 tablets of 5-, 10-, and 25-mg dose strengths will be supplied. Placebo tablets of identical appearance will also be available. Each subject will receive 2 tablets, which combined will make up the required doses of E2609 5, 15, 50 mg, or placebo. The tablets will be supplied by the Sponsor in labeled blister packs. The product release certificates for E2609 and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either E2609 or placebo, or both (see Section 9.4.2.3 for labeling details).

#### 9.4.2.1 Chemical Name and Formula of E2609

- Test drug code: E2609
- Generic name: not applicable
- Chemical name: International Union of Pure and Applied Chemistry
- *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

#### 9.4.2.2 Comparator Drug

Not applicable.

#### 9.4.2.3 Labeling for Study Drug

E2609 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only

- Name and address of the sponsor
- Chemical name/drug identifier (ID)
- Lot number/batch number
- Storage conditions, expiration date if necessary

#### 9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

### 9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups are described in Section 9.4.1. (revised per Amendments 01 and 05)

Randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized blister card identification numbers. At enrollment, the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 3), the IxRS will assign each subject a unique randomization number.

### 9.4.4 Selection of Doses in the Study

It is not known how the level of CSF or brain Aβ reduction is related to clinical efficacy. Therefore, in this study, initial doses will be selected such that at steady state, they will result in 25%, 50%, and 75% reduction in CSF Aβ levels from baseline to cover a broad range of PD effects. (revised per Amendment 06)

In Study 007, the relative bioavailability of a tablet formulation of E2609 in the fed and the fasted states compared with the capsule formulation in the fasted state (used in Studies 001 and 002) was investigated. It was found that when the tablet form of E2609 (50 mg) was administered with food, the exposure (ie, AUC) of the parent drug E2609 was higher, with lower maximum observed concentrations and reduced exposure to the metabolites, compared with either formulation in the fasted state.

Based on the PK/PD modeling using data from healthy volunteer Studies 001, 002, and 007, doses of 5, 15, and 50 mg QD administered as the tablet formulation with food in this study should achieve CSF Aβ reduction from baseline of approximately 25%, 50%, and 75% at steady state, respectively (Table 3).

**Table 3 Predicted Steady State Plasma PK Parameters and CSF Amyloid β Reduction From Baseline**

| E2609 Tablet Daily Dose (mg) With Food | E2609 Plasma $C_{max,ss}$ (ng/ml) | E2609 Plasma $C_{ss,av}$ (ng/ml) | E2609 Plasma $AUC_{(0-24h)ss}$ (ng.h/ml) | % Reduction CSF BACE1 Activity | % Reduction CSF Aβ(1-x) |
|---|---|---|---|---|---|
| 5 | 6.2 | 3.3 | 80.3 | 16.2 | 33 |
| 15 | 18.6 | 10 | 240.9 | 36.6 | 56 |
| 50 | 62.1 | 33.5 | 803.0 | 65.7 | 79 |

Aβ(1-x) = amyloid beta monomer from amino acid 1 to x, $AUC_{(0-24h)ss}$ = area under the concentration x time curve at steady state from time zero to 24 hours, BACE1 = beta-amyloid converting enzyme, CSF = cerebrospinal fluid, $C_{ss,av}$ = average steady-state concentration, $C_{max,ss}$ = maximum plasma concentration at steady state, PK = pharmacokinetics.

The PK/PD modeling described above, which was conducted using data obtained from healthy volunteers, has also been supported by modeling of data from subjects with an underlying AD pathology (Study 101). Furthermore, external data with another BACE1 inhibitor (MK-8931) showed a similar PD effect in AD patients as in healthy volunteers (Forman, et al., 2013). Therefore we are confident that the modeling of E2609 effects in healthy subjects will be applicable for both MCI/Prodromal and mild to moderate AD dementia patients. (revised per Amendment 01)

The exposure of the highest dose in this study (50 mg QD tablet administered with food) is less than that of the 100 mg QD dose (capsule administered fasted) in Study 002.

The 100 mg QD dose administered for 14 days in Study 002 was well tolerated with no clinically significant changes in laboratory parameters, vital signs, or ECG parameters. On Day 15, for the 100 mg QD cohort in Study 002, there was a reduction of CD4 lymphocyte counts compared with placebo (CD4 lymphocyte counts on E2609 decreased by 3.1% from baseline, whereas the placebo control showed an increase of 8.7%), but this decrease was less than that observed at doses of 200 mg (22.9% decrease) or 400 mg (17.3% decrease). No subject had infections or drug rash while receiving E2609 100 mg QD or at lower doses in Study 002, whereas at 200 and 400 mg QD, 4 subjects had symptomatic orolabial HSV1 relapses and 2 subjects at the highest dose had drug rash. The highest dose for Study 202 of 50 mg QD (tablet administered with food) is therefore expected to have a similar or better safety profile compared with the 100 mg QD capsule (administered fasted) in Study 002. Specific exclusion criteria, blinded and unblinded safety monitoring procedures, and safety criteria for discontinuation from study drug are included in this study in order to mitigate any immunology-related risk with E2609, particularly in light of the progression from 14 days of dosing (Study 002) to 18 months of dosing in this study.

Interim analyses of the E2609 plasma PK for all subjects and the E2609 CSF PK and PD profiles will be performed on baseline data and samples collected after at least 4 weeks of treatment. These interim analyses, as well as analyses of safety data, will be performed on an ongoing basis. Refer Section 9.7.3 for more detail. The median and mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment for each dose of E2609 and its 90% confidence interval for the median will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD

data and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline after at least 4 weeks of dosing. (revised per Amendments 01, 02, 03, 04, and 05)

Unblinded interim analyses have indicated E2609 50 mg per day produced relatively high levels of CSF Aβ reduction (greater than 50%) with an acceptable safety profile. As a result, E2609 50 mg has been selected as the dose for Phase 3 development. To gain a more comprehensive safety and tolerability profile of E2609 50 mg, subjects randomized to E2609 5 and 15 mg will be re-assigned to E2609 50 mg for the remaining of the 18-month treatment period with the provision that they will have at least 12 weeks of treatment remaining in the Randomization Phase. (revised per Amendment 06)

### 9.4.5 Selection and Timing of Dose for Each Subject

E2609 is administered orally, QD, with food. Study treatment will begin on Day 1 following randomization and will continue for approximately 78 weeks.

### 9.4.6 Blinding

E2609 and placebo will be administered as tablets of identical appearance.

During the Randomization Phase and Follow-Up Phases, subjects, caregivers/informants, and all clinical site personnel involved with the conduct and interpretation of the study, including investigators will be blinded to the treatment codes (double-blind). In order to make decisions about the remainder of the study as well as the full E2609 clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. (revised per Amendment 03)

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (ie, those who are trained and certified to perform the various cognitive assessments that are undertaken in this study). Furthermore, at the site, the notes and reports relating to safety assessments must be kept separate from the notes and reports relating to efficacy, particularly for the CDR. (revised per Amendment 01)

Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

The PK/PD interim analyses will take place throughout the study as per Amendment 03 and will be conducted by an independent PK/PD scientist at the sponsor. Any additional changes to dose required for this study will be reflected in a further amendment to the protocol and the Statistical Analysis Plan will detail how data will be handled in the primary analysis. (revised per Amendments 02 and 04)

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures

for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

At the conclusion of the study, all unused drug supplies are to be returned to the Eisai approved contract packaging vendor.

### 9.4.7 Prior and Concomitant Therapy

Medication (including over-the-counter medications) or therapy administered to the subject before the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2. Prohibited medications are presented in Listing 1 through Listing 5. Medications that are permitted with restrictions are listed in 6 through Listing 8. (revised per Amendment 04)

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit: (revised per Amendment 04)

- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization

- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization. However, during the treatment period of the study, short term (not more than 14 days) use of steroids up to the equivalent of prednisolone 40 mg once daily is permitted after discussion with the Medical Monitor. Dosing with study drug should be suspended from the time steroid treatment is started. Complete blood count and lymphocyte subsets should be determined prior to starting steroid treatment and continue to be monitored weekly. Study drug may be resumed after discussion with the Medical Monitor when the following conditions are met: (1) treatment with steroids has been completed for at least 1 week; (2) total lymphocytes not <LLN; (3) no lymphocyte subsets are below the discontinuation threshold; (4) the investigator considers that the medical condition which required treatment with steroids has improved or resolved. Weekly testing of lymphocyte subset counts and CBC with differentials is required for 4 weeks following resumption of study drug administration. (revised per Amendment 04)
- (revised per Amendment 06)

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for any efficacy analyses. (revised per Amendment 05)

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed. Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before randomization. They may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 04)
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety, and are not prohibited above. (revised per Amendment 05)

Antiplatelet therapy: (revised per Amendment 04)

- For subjects who consent to CSF sample collection: Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) are permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be

required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

- For subjects who do not consent to CSF sample collection: Aspirin and clopidogrel, individually or in combination, are permitted.

### 9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period. CRAs will review treatment compliance during site visits and at the completion of the study.

### 9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the principal investigator including a copy of the principal investigator's current medical license (required for United States sites) or medical registration number on the curriculum vitae
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

## 9.5 Study Assessments

### 9.5.1 Assessments

#### 9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

#### 9.5.1.2 Baseline Assessments

Assessments to be made at Screening and Baseline and throughout the study are described in Section 9.5.1.3, Section 9.5.1.4, and Section 9.5.1.5.

##### 9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, current medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment due to AD. Subjects will be asked about history of TB, infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV Types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include onset, duration, relapse frequency, severity, and treatments. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The 15-item GDS and modified Hachinski ischemic scale will also be assessed at Screening as part of the exclusion criteria.

Physical examinations (complete or routine) will be performed as designated in Table 6 and Table 7. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, and skin, and a neurological examination (including the Brief Smell Identification Test [Sensonics Inc.]). (revised per Amendment 04). A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

##### 9.5.1.2.2 VIRAL TESTING

As specified in Table 6, blood will be collected for screening for Hepatitis B and Hepatitis C for determining eligibility, and at Baseline for viral characterization.

##### 9.5.1.2.3 B12 TESTING

Blood will also be collected for vitamin B12 levels as specified in Table 6.

#### 9.5.1.2.4 TB EXPOSURE TESTING

Blood will also be collected for testing for previous TB exposure, as specified in Table 6.

#### 9.5.1.2.5 URINE DRUG TESTING

Urine will be collected for drug screening as specified in Table 6.

### 9.5.1.3 Efficacy Assessments

#### 9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

The timing of psychometric assessments is shown in Table 6 and Table 7. These assessments should be administered in the morning (or, if not possible, consistently at the same time of day) and should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). At the Screening Visit, the recommended order of assessments is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. At the Baseline Visit, the assessments are to be conducted in the following order: MMSE, CDR, ADAS-cog$_{14}$, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). (revised per Amendment 02)

At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

**Alzheimer's Disease Assessment Scale - cognitive subscale:** Discussed in Section 9.2.3. (revised per Amendment 05)

**Clinical Dementia Rating:** The CDR assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

**Mini Mental State Examination:** A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

**ISLT:** The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects will read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 15 minutes, in which time the CBB is performed, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

**CogState Brief Battery:** The CBB is a computer-based battery comprising 4 cognitive tests:

- Detection – a simple reaction time test where the subject presses a key when the card is turned face up from a pack of cards ("Has the card turned over"). Speed of response is the measure.
- Identification – a simple choice reaction time test where the subject presses 1 of 2 keys when the card just turned face up is either a red card or a black card ("Is the card red"). Speed of response is the measure.
- One Card Back – a simple working memory test where the subject presses 1 of 2 keys when the card turned face up is either the card seen in the immediately previous trial or not ("Is the previous card the same"). Accuracy of response is the measure.
- One Card Learning – a visual learning and memory test where the subject presses 1 of 2 keys depending on whether the card just turned face up has been seen before or not in the task ("Have you seen this card before in this task"). Accuracy of response is the measure.

**Functional Assessment Questionnaire:** The caregiver or informant provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent). (revised per Amendment 04)

#### 9.5.1.3.2 VOLUMETRIC MRI

Volumetric MRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the Alzheimer's Disease Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

Volumetric MRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. Volumetric MRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. Volumetric MRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 6 and Table 7, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

For subjects who consent to CSF sample collection, CSF samples will be collected by LP (gravity drip method) at the timepoints specified in Table 6 and Table 7 (revised per Amendment 02). The CSF sample taken at the Baseline Visit will only be performed after subjects consent to CSF sample collection, and after confirmation of an amyloid positive PET scan (revised per Amendment 02). See Section 9.5.1.4.2 for further details.

### 9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

#### 9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of E2609. For subjects who consent to CSF sample collection, CSF samples will be collected for the determination of E2609 concentrations. (revised per Amendment 02) Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with E2609.

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 6 and Table 7. Two PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visits 5, 11, 14, and 16, and 4 to 8 hours postdose at Visit 7 and Visit 18 (or at the ED Visit). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug with food at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or at the ED Visit) the PK blood sample should be collected shortly before or shortly after completing the LP. (revised per Amendment 01) Although the PK sampling procedures at the ED visit should follow those of Visit 18, in the event that study drug has already been discontinued prior to the ED visit, then no dosing will be conducted. However, a PK sample at trough (before LP) will be collected, followed by LP at approximately the same time as previous visits. A 2nd PK blood sample will be collected as close as possible in time to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

Blood will also be drawn where possible at the 1st report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

#### 9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

**Biomarkers**

Subjects who consent to CSF sample collection will be encouraged to stay at the site after completion of LP for medical observation (revised per Amendment 02). At Baseline, a CSF sample will be collected by LP (gravity drip method) after fasting (preferred), or at least 2 hours after the most recent meal (Section 9.5.1.3.3). The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 [or later postrandomization timepoint] and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. (revised per Amendment 04) At visits where cognitive tests are also performed, if the tests are to be performed on the same day, the LP must be performed after the cognitive tests have been completed and the subjects should rest and drink some fluid to hydrate before the LP. (revised per Amendment 01) The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. The CSF sample will be used for PD assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 levels and activity. (revised per Amendment 04)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to

postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The pre- and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendment 04) BACE1 levels will be measured using internally developed fluorescence resonance energy transfer and ELISA based assay(s). Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

The blood sample collected for PD analyses at Baseline should be collected on the same day shortly before or shortly after completing the LP at Baseline. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

At the Baseline Visit, blood samples will be collected and stored for determination of prior exposure to any suspected infective agents in the event that the subject develops treatment-emergent AEs that warrant further investigation (eg, treatment-emergent infection). For subjects who consented to CSF sample collection, CSF samples from the Baseline Visit will also be stored for the same purpose. (revised per Amendment 02) Testing may include, but not be limited to, serological tests, viral titer by quantitative polymerase chain reaction, or human leukocyte antigen genotyping.

Blood samples will be collected for PD assessments as specified in Table 6 and Table 7. See Section 9.5.1.4.2 for further details.

For all subjects, baseline and on-study blood samples, DNA samples, and any CSF samples collected from subjects who consent to CSF collection will be stored for up to 15 years. (revised per Amendment 02)

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

**Pharmacogenomics**

A blood sample will be obtained at Baseline and will be used to determine the *ApoE* genotype (homozygous or heterozygous E4 versus non-E4) and the *NAT2* phenotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response, safety, or PK of E2609. Details of which genotype / phenotype data will be applied to the analyses of efficacy, safety or PK will be discussed in the Statistical Analysis Plan.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the

development of AEs, or underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

**Amyloid PET**

An amyloid PET scan will be performed at Screening to confirm deposition of amyloid in the brain. An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02) Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses) (Table 6). (revised per Amendments 02 and 05) PET scanning will be performed with a locally approved Aβ imaging agent (eg, Amyvid). Descriptions and detailed instructions for all imaging can be found in the imaging manual.

Amyloid PET imaging is an exploratory measure of the potential disease-modifying effects of E2609.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, lymphocyte subsets, Igs, and urine values; periodic measurement of vital signs and ECGs; performance of physical and neurological examinations; centralized dermatological assessments; the C-SSRS; and safety MRIs as detailed in Table 6 and Table 7 will also be conducted. Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and post-treatment for exploratory immunomodulatory and immune-based analyses.

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (see Section 9.4.6). (revised per Amendment 01)

##### 9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E2609.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product,

whether or not considered related to the investigational product (Note: It is not necessary to report every sign or symptom as a separate AE if the overall disease [diagnosis] is being reported as an AE.)

- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, discontinuation of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 20, as shown in Table 7). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF. SAEs will be collected for 3 months after the last dose of study drug, ie, through to the final Follow-Up visit (Visit 20). However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures. (revised per Amendments 04 and 05)

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the ADAS-cog$_{14}$, MMSE, ISLT and CBB (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 4.

- Euphoric mood
- Elevated mood

- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis
- Dissociative state

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.11 for a description of the C-SSRS).

The following AEs will require the collection of information sufficient to provide a detailed description of the event, treatment and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection; any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a "yes" answer to Type 4 or 5 suicidal ideation, or a "yes" response to any suicidal behavior on the C-SSRS.

All AEs must be followed through the final Follow-Up visit (Visit 20), or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. (revised per Amendment 04)

**Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.**

### Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

| | |
|---|---|
| Mild | Discomfort noticed, but no disruption of normal daily activity |
| Moderate | Discomfort sufficient to reduce or affect normal daily activity |
| Severe | Incapacitating, with inability to work or to perform normal daily activity |

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

## Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

*Classification of Causality*

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

#### 9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reportable using the criteria of important medical event if the event does not meet other serious criteria: new onset seizures, ocular herpes.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the eCRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

#### 9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 4. Subjects should be in a seated or supine position during blood collection. Table 6 and Table 7 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

See Section 9.3.3 for safety criteria for discontinuation from study drug related to absolute counts of CD4, CD8, and B lymphocytes, and for lymphocyte subset counts.

## Table 4 Clinical Laboratory Tests

| Category | Parameters |
|---|---|
| **Hematology** | Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils).<br><br>PT, PTT, and INR (Screening and Baseline only) (revised per Amendment 02) |
| **Chemistry** | |
| **Electrolytes** | Bicarbonate, calcium, chloride, phosphate, potassium, sodium |
| **Liver function tests** | Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin |
| **Renal function tests** | Blood urea/blood urea nitrogen, creatinine |
| **Other** | Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid |
| **Urinalysis** | Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells |
| **Other** | Lymphocyte T and B cell subset analyses (see Table 5). Regulatory T cells (revised per Amendment 04)<br>PBMCs (revised per Amendment 02)<br>Ig analyses (IgG, IgA, and IgM).<br>Viral screen (HCVAb [Hepatitis C] and HbsAg [Hepatitis B]).<br>Viral characterization (including HSV1, HSV2 and CMV, etc)<br>Serum pregnancy test (females of child bearing potential only)<br>Tuberculosis Interferon Gamma Release Assays<br>Tests for thyroid function (thyroid stimulating hormone, free triidothyronine and free thyroxine) and vitamin B12<br>Blood sample for storage for subsequent testing of immune status<br>Cerebrospinal fluid sampling |

Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials must also be repeated. (revised per Amendment 02)

CMV = cytomegalovirus, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV = herpes simplex virus, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PT = prothrombin time, PTT = partial thromboplastin time.

The 8 different surface markers (including but not limited to CD3, CD4, CD8, CD45, CD19, CD16, CD56, and CD14) and total lymphocyte counts will be measured in order to provide the lymphocyte subset data as shown in Table 5. In addition, Regulatory T cells will be measured. Current sponsor data supports the literature showing there is an age-related decline in lymphocyte subsets (see Appendix 5). These data have been used to revise the LLNs for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts to the population-adjusted LLNs of 396, 157, and 74 cells/µL, respectively) (revised per Amendments 02 and 04).

**Table 5 Lymphocyte Subtypes Inclusive in BD Trucount™**

| Cell Type | Cell Surface Markers |
|---|---|
| T lymphocytes | CD3 |
| T helper cells | CD3+, CD4 |
| Cytotoxic T cells | CD3+, CD8 |
| Mature B cells | CD3-, CD19 |
| Natural killer cells | CD3-, CD16, CD56 |
| Macrophages | CD14 |

(Table 5 revised per Amendment 04)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the case report form [CRF] Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

#### 9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [bpm], respiratory rate [per minute], body temperature [in centigrade], and weight [kg]) will be obtained at the visits designated in Table 6 and Table 7 by a validated method. Measurements of sitting BP and heart rate will be obtained. All BP measurements should be performed on the same arm, preferably by the same person.

#### 9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination will be performed at Screening as described in Section 9.5.1.2.1. At Baseline and during the Randomization Phase, routine physical examinations will take place as shown in Table 7. These examinations will include the cardiovascular system, respiratory system, and neurological system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 6 and Table 7. Twelve-lead standard ECGs will be recorded in triplicate (1 minute apart) after subjects have been resting

in the supine position for at least 5 minutes.

On any study day when ECG, vital signs, and blood samples are taken, these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.7 SAFETY MRI

Safety brain MRI assessments will be performed at the times shown in Table 6 and Table 7. Additional safety MRI scans can be performed at unscheduled visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Safety MRIs will be acquired using a standardized procedure that will include fluid-attenuated inversion recovery (FLAIR), gradient-echo, T1, and diffusion-weighted sequences to determine the presence of focal lesions including, but not limited to, evidence for ischemic and hemorrhagic stroke, subdural hematoma, neoplasm, arteriovenous malformation, micro and macrohemorrhages, superficial siderosis, lacunar infarcts, white matter abnormalities, and vasogenic edema. The imaging sequence for the Screening/safety MRI will include: T2 weighted anatomic MRI to rule out major white matter changes, cerebral infarction or other structural lesions, and a high-resolution 3D T1-weighted scan with isotropic voxels with volumes of 1 $mm^3$ or less. In addition, both FLAIR for the detection of vasogenic edema and T2 Gradient Recall Echo for the detection of microhemorrhages will be acquired. The 3D dataset will be reconstructed in transverse slices in Digital Imaging and Communications in Medicine format. The results of this MRI assessment will also be used as the Baseline Period MRI, against which changes after drug administration will be compared. Further details of the MRI protocol can be found in the Imaging Acquisition Guideline. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, and 18 and at the final Follow-Up Visit (Visit 20). (revised per Amendment 04) In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

At any time during the treatment period, subjects will be discontinued from study drug if they develop any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. All of these features must be reported as study specific AEs (or AEs of special interest). These subjects will undergo an ED Visit within 7 days after discontinuation and 4 Follow-Up Visits at 2, 4, 8 and 12 weeks after the last dose of treatment. (revised per Amendment 04) Subjects will also undertake an

Unscheduled Visit (with MRI) at approximately 30 days after the visit at which such MRI features were first identified. Additional visits may be arranged if clinically indicated in the opinion of the investigator, and may occur later than 12 weeks after the final dose of study drug.

#### 9.5.1.5.8 DERMATOLOGIC ASSESSMENT

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at the times shown in Table 6 and Table 7. These assessments will specifically include evaluation of any areas of depigmentation or any rash.

In addition, subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregiver or informants will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or infection, and the investigator will be required to review such AEs as soon as possible and consider an unscheduled physical and dermatological evaluation. Detailed characteristics of any skin rashes will be captured in the clinical database. Physical examination may be undertaken where indicated. Treatment-emergent abnormal dermatological findings should be reported as AEs.

#### 9.5.1.5.9 NEUROLOGIC EXAMINATION

Neurological examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations as shown in Table 6 and Table 7. Details of these examinations will be captured in an eCRF. The neurological examinations will monitor for new symptoms and signs which will then alert the investigator to consider new CNS pathology (especially slowly-evolving neurological conditions that may not lead to prominent symptoms). Examples of neurological signs that may indicate new CNS pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. In such a situation, the investigator should consider (but not limited to) demyelination in the differential diagnoses, and should discuss with the sponsor's medical monitor further investigations or treatment, which will be decided case by case. Neurological examinations will also include the assessment of cranial nerve function, especially the olfactory nerve; the Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits to objectively test olfaction. Treatment-emergent abnormal neurological findings should be reported as AEs.

#### 9.5.1.5.10 PREGNANCY TEST

At Screening, females of childbearing potential will have a serum pregnancy test. At Baseline and during the Treatment Period, urine samples will be obtained from females of childbearing potential for pregnancy tests (see Table 7).

#### 9.5.1.5.11 COLUMBIA SUICIDE SEVERITY RATING SCALE

An assessment of suicidal ideation and behavior using the C-SSRS will be performed at the designed time points in Table 6 and Table 7. A "yes" answer to Type 4 or 5 suicidal ideation or a "yes" response to any suicidal behavior queries will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

#### 9.5.1.5.12 BIOMARKER SAMPLES

As noted in Section 9.5.1.4.2, CSF (for subjects who consent to CSF sample collection), blood, and DNA samples will be collected and may be used for exploratory biomarker analyses, as well as tested in the event that a subject develops AEs that warrant further investigation. (revised per Amendment 02)

#### 9.5.1.5.13 OPHTHALMIC EXAMINATIONS

An ophthalmic examination will be conducted at Baseline (unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available). An additional examination will be conducted, if the subject experiences visual disturbances during the course of the study or is medically indicated. The ophthalmic examinations should include fundoscopy to look at the optic disc, macula and the rest of the retina, as well as an assessment of visual acuity and visual fields.

### 9.5.2 Schedule of Procedures/Assessments

#### 9.5.2.1 Schedule of Procedures/Assessments

Table 6 presents the Schedule of Procedures/Assessments for the Prerandomization Phase. Screening assessments will be organized into 4 tiers (see below and Figure 2).

Table 7 presents the Schedule of Procedures/Assessments for the Randomization Phase.

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

| Phase | Prerandomization | |
|---|---|---|
| Period | Screening | Baseline |
| Visit | 1 | 2 |
| **Procedures/Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)** | | |
| Informed consent (subject and caregiver or informant) | X (Tier 1) | |
| Subject informed consent for CSF sample collection (voluntary)[a] | X | X |
| Demographics | X (Tier 1) | |
| Medical history[b] | X (Tier 1) | |
| Prior / concomitant medications[c] | X (Tier 1) | X |
| Vital signs including weight[d] | X (Tier 1) | X |
| Height | X (Tier 1) | |
| Complete physical examination | X (Tier 1) | |
| Routine physical examination | | X |
| CBB and ISLT[e] | X (Tier 1) | X |
| MMSE[e] | X (Tier 1) | X |
| CDR[e] | X (Tier 1) | X |
| FAQ[e] | X (Tier 1) | X |
| ADAS-cog$_{14}$[e] | | X |
| 15-item Geriatric Depression Scale | X (Tier 2) | |
| Modified Hachinski ischemic scale | X (Tier 2) | |
| C-SSRS | X (Tier 2) | X |
| 12-lead ECG[f] | X (Tier 2) | X |
| Blood and urine for clinical laboratory tests[g] | X (Tier 2) | X |
| Blood for lymphocyte subset analyses[h] | X (Tier 2) | X |
| Blood for Ig analyses[i] | X (Tier 2) | X |
| Blood for viral screen[j] | X (Tier 2) | |
| Blood for thyroid function tests[k] | X (Tier 2) | |
| Blood for vitamin B12 test | X (Tier 2) | |
| Test for previous TB exposure | X (Tier 2) | |
| Urine drug screen | X (Tier 2) | |
| Serum pregnancy test (females of childbearing potential only) | X (Tier 2) | |
| Urine pregnancy test (females of childbearing potential only) | | X |
| Safety and Volumetric MRI[l] | X (Tier 3) | |
| Amyloid PET scan[m] | X (Tier 4) | |
| Inclusion and Exclusion criteria | X (All tiers) | X |
| Adverse events | X (All tiers) | X |
| CSF sampling for PK, PD and storage[a] | | X |
| Blood sample for PK assessments[n] | | X |
| Blood sample for PD and exploratory biomarker assessments[o] | | X |
| Blood sample for pharmacogenomics | | X |
| Blood sample for storage for immune status[p] | | X |
| Blood sample for PBMC isolation | | X |
| Blood sample for viral characterization[q] | | X |
| Centralized dermatological assessment via photography[r] | | X |
| Neurological examinations[s] | | X |
| Ophthalmic assessment[t] | | X |

(Table revised per Amendments 02 and 04)

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

AChEI = acetylcholinesterase inhibitor, AD = Alzheimer's disease, ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CDR = Clinical Dementia Rating, CMV = cytomegalovirus, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), Ig = immunoglobulin, INR = International Normalized Ratio, ISLT = International Shopping List Task (immediate and delayed recall), LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetics, PET = positron emission tomography, PT = prothrombin time, PTT = partial thromboplastin time, TB = tuberculosis.

Note: Screening assessments/procedures have been organized into 4 distinct tiers. All assessments and procedures in each tier should be completed (see Figure 2), and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures, as long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. Similarly, all screening assessments and procedures must be completed, and eligibility to continue in the study confirmed, before any baseline assessments and procedures commence. Adverse events and eligibility against inclusion and exclusion criteria must be assessed at each stage within the Screening Visit and at the Baseline Visit. (revised per Amendment 01)

Note: All screening and baseline assessments are to be completed within 50 days, plus an additional window of up to 30 days if required (revised per Amendment 02). The interval between availability of the results of the last screening assessment (PET scan) and the first baseline (Visit 2) assessments should be as short as possible and ideally should not exceed 7 days. Visit 3 (Randomization) (see Table 7) should occur no more than 10 days after completion of the Baseline visit (Visit 2) and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion No.20 into account (revised per Amendment 02). Thus, the total Prerandomization Phase may be up to 60 days, plus an additional window of up to 30 days if required (revised per Amendment 02).

a: Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. For those subjects who do consent to CSF sample collection: CSF will be collected by LP after fasting (preferred), or at least 2 hours after the most recent meal. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 [or later postrandomization timepoint] and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. If the LP and cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. The CSF sample will be used for PK and PD assessments. A CSF sample will also be stored for testing in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). (revised per Amendments 01, 02, and 04)

b: To include: mild cognitive impairment and AD history; history of TB, vaccination history against and infections due to varicella zoster virus (chickenpox and herpes zoster or shingles); infections due to HSV1 (orolabial herpes or cold sores) and 2 (genital herpes). Medical history of infections to include: onset, duration, relapse frequency, severity, and treatments. For any active infection within the last 4 weeks prior to randomization, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)

c: Prior and concomitant medications include AChEIs and memantine, and other medications for cognitive decline.

d: Weight, respiratory rate, body temperature, and sitting blood pressure and heart rate will be obtained.

e: To be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). At the Screening Visit, the recommended order of assessments is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. At the Baseline Visit, the assessments are to be conducted in the following order: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). (revised per Amendment 02) At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

f: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

g: Clinical laboratory tests consist of hematology (including PT, PTT, and INR), clinical chemistry, and urinalysis.

h: Lymphocyte subsets will include but are not limited to the following cell surface marker assessments: CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cells), CD16/CD56 (natural killer cells) and CD14 (macrophages). Regulatory T cells will also be measured. Viability staining may also be employed. Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials, must also be repeated. (revised per Amendments 02 and 04)

i: Igs to be analyzed include IgG, IgA and IgM.

j: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

k: Thyroid function tests include thyroid stimulating hormone, free triidothyronine, and free thyroxine.

l: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images. MRI will be read by an approved central reader. Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session. (revised per Amendment 01)

m: PET scanning will be performed with a locally approved β-amyloid imaging agent, eg, Amyvid if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. The PET image will be centrally read for the purpose of determining eligibility for inclusion into the study. An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02)

n: The PK blood sample should be collected on the same day shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

o: The PD and exploratory biomarker blood sample should be collected shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

p: A blood sample will be collected at Baseline and stored. This sample may be used for exploratory biomarkers associated with study drug or disease, or in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

q: Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

r: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. See Section 9.5.1.5.8 for further details.

s: To be performed by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. Section 9.5.1.5.9 details what is included in the neurological examination. The Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits and serves as part of the neurological examination. (revised per Amendment 04)

t: An ophthalmic examination will be conducted at Visit 2 unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available. The ophthalmic examination should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields.

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| Phase | Randomization | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Period | Treatment | | | | | | | | | | | | | | | | | Follow-Up | | | | | |
| Visit[a] | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | ED[b] | W2 | 19[c] | W8 | 20[c] | UNS Visit[d] | Interim Safety Visit |
| Day | 1 | 8 | 15 | 22 | 29 | 43 | 57 | 71 | 85 | 113 | 141 | 183 | 274 | 365 | 456 | 547 | | 561 | 575 | 589 | 631 | | |
| Week | 1 | 2 | 3 | 4 | 5 | 7 | 9 | 11 | 13 | 17 | 21 | 27 | 40 | 53 | 66 | 79 | | 81 | 83 | 87 | 91 | | |
| Weeks elapsed since first dose | 0 | 1 | 2 | 3 | 4 | 6 | 8 | 10 | 12 | 16 | 20 | 26 | 39 | 52 | 65 | 78 | | 80 | 82 | 86 | 90 | | |
| Nominal months elapsed since first dose | 0 | | | | 1 | | 2 | | 3 | 4 | 5 | 6 | 9 | 12 | 15 | 18 | | | 19 | | 21 | | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | | | | |
| Routine physical examination | X | | | | X | | X | | X | | | X | X | X | X | X | X | | X | | X[e] | X | |
| Inclusion and Exclusion criteria | X | | | | | | | | | | | | | | | | | | | | | | |
| Vital signs[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X[e] | X | X |
| Respiratory rate | | | | | X | | X | | X | X | X | X | X | X | X | X | X | | X | | X[e] | X | |
| Weight | | | | | | | | | X | | | X | X | X | X | X | X | | | | X | X | |
| Centralized dermatological assessment via photography[g] | | | | | | | | | X | | | X | X | X | X | X | X | | | | X | X | |
| Neurological examination[h] | | | | | | | | | | | | X | | X | | X | X | | X | | X | X | |
| Ophthalmic examination[i] | | | | | | | | | | | | | | | | | | | | | | X | |
| Concomitant medications[j] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | X | X |
| 12-lead ECG[k] | | | X | | X | | X | | X | | | X | | X | | X | X | | X | | X[e] | X | |
| Clinical biochemistry and urinalysis | | | X | | X | | X | | X | | | X | X | X | X | X | X | | X | | X | X | |
| Complete blood count | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[l] | X |
| Blood samples (lymphocyte subset analyses)[l] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[l] | X |
| Blood samples (Igs)[m] | | | | | X | | X | | X | | | X | | X | | X | X | | X | X | X | X | |
| Blood samples (isolation of PBMCs) | | | X | | | | | | X | | | | | | | | | | | | X | | |
| Urine pregnancy test (females of CBP only) | X[n] | | | | | | | | X | | | X | X | X | X | X | X | | X | | | X | |
| Blood sample (storage for immune status)[o] | | | | | X | | | | X | | | X | | X | | X | X | | X | | X | X | |
| CBB and ISLT[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | | |
| MMSE[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | | |
| CDR[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | | |
| ADAS-cog$_{14}$[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | | |

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| **Phase** | **Randomization** | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | | | | | **Follow-Up** | | | | | |
| **Visit**[a] | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **ED**[b] | **W2** | **19**[c] | **W8** | **20**[c] | **UNS Visit**[d] | **Interim Safety Visit** |
| **Day** | **1** | **8** | **15** | **22** | **29** | **43** | **57** | **71** | **85** | **113** | **141** | **183** | **274** | **365** | **456** | **547** | | **561** | **575** | **589** | **631** | | |
| **Week** | **1** | **2** | **3** | **4** | **5** | **7** | **9** | **11** | **13** | **17** | **21** | **27** | **40** | **53** | **66** | **79** | | **81** | **83** | **87** | **91** | | |
| **Weeks elapsed since first dose** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **10** | **12** | **16** | **20** | **26** | **39** | **52** | **65** | **78** | | **80** | **82** | **86** | **90** | | |
| **Nominal months elapsed since first dose** | **0** | | | | **1** | | **2** | | **3** | **4** | **5** | **6** | **9** | **12** | **15** | **18** | | | **19** | | **21** | | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | | | | |
| FAQ[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | | |
| C-SSRS | | | | | X | | X | | X | | | X | X | X | X | X | X | | X | | X[e] | X | |
| Safety and Volumetric MRI[q] | | | | | | | | | | | | X | | X | | X | X | | | | X | X | |
| Amyloid PET[r] | | | | | | | | | | | | | | | | X | X | | | | | | |
| Telephone contact[s] | | | X | | X | | | | X | | | X | | X | | X | X | | | | | X | |
| Blood samples for PK[t] | | | X | | X | | | | X | | | X | | X | | X | X | | | | | X | |
| Blood samples for PD and exploratory biomarkers[u] | | | X | | X | | | | X | | | X | | X | | X | X | | X | | X | | |
| CSF sampling for PK and PD[v] | | | | | X | | | | | | | | | | | X | X | | | | | X | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[l] | X |
| Sleep/dream questionnaire[w] | | | | | | | | | | | | | | | | | | | | | | X | |
| Randomization | X | | | | | | | | | | | | | | | | | | | | | | |
| Dispense study drug[x] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | | | |

**Footnotes for Table 7**

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating scale, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), Ig = immunoglobulin, ISLT = International Shopping List Task, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, UNS = unscheduled, W2 = new Week 2 follow-up visit, W8 = new Week 8 follow-up visit. (revised per Amendment 04)

a: Visit 3 should be conducted no more than 10 days after completion of the Baseline visit (Visit 2) assessments and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion #20 into account. (revised per Amendment 02) A window of ±3 days will be permitted for Visit 4 to 14 inclusive. A window of ±10 days will be permitted for Visit 15 to 18 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since first dose" at subsequent visits.

b: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug (Visit W2, 19, W8, and Visit 20, respectively). (revised per Amendments 04 and 05)

c: All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 4 post-treatment Follow-Up visits; 2, 4, 8, and 12 weeks after the last dose of study drug (Visits W2, 19, W8, and 20, respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the post-treatment Follow-Up period. (revised per Amendment 04)

d: Unscheduled visits may be conducted at any time that safety or safety MRI data indicate per protocol or as clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

e: Only if clinically significant abnormalities are found at Visit 19 and the investigator considers it necessary to repeat at Visit 20. Clinical biochemistry, urinalysis, CBC, lymphocyte subsets and Igs should always be performed at Visit 20, regardless of clinical significance at the previous Follow-Up visit. (revised per Amendments 02 and 04)

f: Measurements of body temperature and sitting blood pressure and heart rate will be obtained.

g: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. Additional UNS dermatological assessments should be conducted in response to any dermatological AEs of concern (eg, depigmentation, rash, herpetic lesion).

h: Examples of neurological signs that may indicate new central nervous system pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. The Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits and serves as part of the neurologic examination. (revised per Amendment 04)

i: If the subject experiences visual disturbances during the course of the study, the subject will be referred to a specialist for a further ophthalmic examination, which should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields

j: Please refer to Section 9.4.7, which details prohibited and permitted medications in the study and associated timeframes.

k: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

l: Lymphocyte subsets will include but are not limited to the following cell surface marker assessments: CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [NK cells] and CD14 [macrophages]) and total lymphocytes. Regulatory T cells will also be measured. Viability staining may also be employed. Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a Complete Blood Count, with differentials, must also be performed along with assessment of AEs. (revised per Amendments 02 and 04)

**Footnotes for Table 7**

m: Igs to be analyzed include IgG, IgA, and IgM.

n: An additional assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

o: Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops a TEAE that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

p: These assessments are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The order of assessments will be: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). At visits where the CDR or FAQ are conducted, the investigator will determine whether the informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

q: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images in MRI will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, 18, and 20. In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A volumetric MRI sequence will be collected in all subjects immediately following all safety MRI assessments. (revised per Amendment 01)

r: PET scanning will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks. A PET scan will only be performed at Visit 18 or ED if the subject has a valid Screening PET scan for the purposes of longitudinal analyses; subjects who were determined to be eligible for the study on the basis of an historical PET scan will not have a PET scan performed at Visit 18 or ED (revised per Amendment 02)

s: Site staff will contact the subject or the caregiver or informant the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the caregiver or informant, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

t: Two plasma PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visit 5, Visit 11, Visit 14, and Visit 16 and 4 to 8 hours postdose at Visit 7 and Visit 18 (or ED). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or ED) the PK blood sample should be collected shortly before or shortly after completing the LP. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected, followed by LP at approximately the same time as at previous visits. A second PK blood sample will be collected as close as possible to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

u: PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day. At Visits 5, 11, 14, and 16 the PD blood samples should be collected predose.

v: For subjects who consent to CSF sample collection: Postrandomization CSF sample collection is scheduled at Visit 7 (or later postrandomization timepoint) and Visit 18/ED. If a postrandomization CSF sample is collected later than Visit 7, time-matched plasma PK samples are also required (see Footnote t). All visits at which CSF samples are scheduled to be taken also include blood PK and PD assessments and so the subject will be dosed at the clinic on these days. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 [or later postrandomization timepoint] and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If the LP and the cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already

**Footnotes for Table 7**

stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. . Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendments 01, 02, and 04)

w: Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

x: The first dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time as determined by the PI or Safety Physician for postdose medical observation. (revised per Amendment 02)

#### 9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 6 and Table 7 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 4 tiers (see Table 6, Section 9.5.2, and Figure 2.

See Section 9.5 for a full description of the procedures and assessments to be performed during this study.

Table 8 presents the number of blood and CSF samples, and the total volume of blood and CSF that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety.

**Table 8 Summary of Blood and CSF Sample Volumes**

| Assessment | Total number of collection time points | Number of time points x volume per collection (mL whole blood or CSF) | | Total volume (mL whole blood or CSF) |
|---|---|---|---|---|
| | | Screening and Baseline Periods | Treatment and Follow-Up Periods | |
| **Blood** | | | | |
| Chemistry | 12 | 2 x 2 mL | 10 x 2 mL | 24 mL |
| Hematology | 20 | 2 x 5 mL | 18 x 5 mL | 100 mL |
| Lymphocyte subset analyses[a] | 20 | 2 x 4 mL | 18 x 4 mL | 80 mL |
| PBMC | 4 | 1 x 16 mL | 3 x 16 mL | 64 mL |
| IgA, IgM, IgG | 10 | 2 x 2 mL | 8 x 2 mL | 20 mL |
| PT, PTT for INR | 2 | 2 x 3 mL | None | 6 mL |
| Thyroid function tests (thyroid stimulating hormone, free triidothyronine and free thyroxine) | 1 | 1 x 3 mL | None | 3 mL |
| Viral screen (Hepatitis B and C) | 1 | 1 x 4 mL | None | 4 mL |
| Viral characterization | 1 | 1 x 4 mL | None | 4 mL |
| Vitamin B12 | 1 | 1 x 2 mL | None | 2 mL |
| Serum pregnancy test | 1 | 1 x 2 mL | None | 2 mL |
| Tuberculosis (interferon-gamma release assays) | 1 | 1 x 3 mL | None | 3 mL |
| Sample for immune status | 8 | 1 x 4 mL | 7 x 4 mL | 32 mL |
| PD sample | 9 | 1 x 4 mL | 8 x 4 mL | 36 mL |
| PK analysis | 7 | 1 x 3 mL | 6 x 6 mL | 39 mL |
| Pharmacogenetic sample | 1 | 1 x 3 mL | None | 3 mL |
| All blood samples, total volume whole blood collected | | 80 mL | 342 mL | 422 mL |
| **CSF (For subjects who consent to CSF sample collection) (revised per Amendment 02)** | | | | |
| PD and PK samples | 3 | 1 x 12 mL | 2 x 12 mL | 36 mL |

CSF = cerebrospinal fluid, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetic, PT = prothrombin time, PTT = partial thromboplastin time.

a: Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials must also be performed. Therefore, for each unscheduled or repeat test, an additional 9 mL will be collected (5 mL for hematology and 4 mL for lymphocyte subset analyses)

(Table 8 revised per Amendment 04)

### 9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include vital signs, clinical laboratory assessments, physical examinations, ECG measurements, and reports of AEs. MRI will be used to detect vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage and is a standard evaluation to ensure subject safety. The C-SSRS has been endorsed by the FDA as a measure of potential suicidality (Guidance for Industry Suicidality).

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, in addition to mitigating clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. Details are provided in Section 9.2.5.

### 9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

#### 9.5.4.1 Reporting of Serious Adverse Events

**All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.**

SAEs, regardless of causality assessment, must be collected up to 3 months after the last dose of study drug, ie, through to the final follow-up visit (Visit 20). (revised per Amendment 04) (revised per Amendments 04 and 05) However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

**For urgent safety issues**, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

#### 9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must discontinue study treatment.

#### 9.5.4.3 Reporting of Events Associated with Special Situations

##### 9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

| | |
|---|---|
| Overdose | Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose |
| Misuse | Intentional and inappropriate use of study drug not in accordance with the protocol |
| Abuse | Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects |
| Medication error | Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject |

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

##### 9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2) should always be considered serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

#### 9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

#### 9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

#### 9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

### 9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue study drug or withdraw from the study at any time for any reason. All subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug (Visits W2, 19, W8, and Visit 20, respectively) (see Section 9.1.2.3). (revised per Amendment 04) See Table 7 for full details of the assessments to be performed at these visits. revised per Amendment 05) Subjects who discontinue study drug early (as opposed to subjects whose dosing with study drug is temporarily suspended under Medical Monitor guidance) will not be permitted to restart study drug.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and will provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who withdraw prematurely from the study will be withdrawn for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for withdrawal from the study. Study disposition information will be collected on the Subject Disposition eCRF.

A subject removed from the study for any reason may not be replaced.

### 9.5.6 Abuse or Diversion of Study Drug

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF. (revised per Amendment 04)

### 9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

## 9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

### 9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

### 9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy assessments performed in this study.

## 9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance. (revised per Amendment 05)

### 9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Analyeses will be performed based on treatment group, which will be defined in the statistical analysis plan (SAP). Additional analyses related to dose re-assignment will be performed for subjects who will be switched from E2609 5 mg and 15 mg to E2609 50 mg. Further details will be provided in the SAP, which will be finalized before database lock. (revised per Amendment 06)

#### 9.7.1.1 Study Endpoints

##### 9.7.1.1.1 PRIMARY ENDPOINT

- Safety and tolerability, which include incidence of TEAEs and SAEs, laboratory parameters, vital signs, and ECG parameters (revised per Amendment 05)

##### 9.7.1.1.2 SECONDARY ENDPOINTS

(revised per Amendments 02 and 05)

- % reduction of Aβ(1-x) and Aβ(1-42) in CSF relative to baseline after from 4 weeks and up to 18 months of treatment

- The population PK parameters of E2609 in CSF and plasma, including the effect of intrinsic and extrinsic factors (including NAT2 phenotype)

#### 9.7.1.1.3 EXPLORATORY ENDPOINTS

(revised per Amendments 01, 02, 04, and 05)

Change from baseline in:

- CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) after at least 4 weeks and at 18 months of treatment
- CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment (revised per Amendment 06)
- Total hippocampal volume at 12 and 18 months of treatment as measured by vMRI
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months of treatment as measured by vMRI
- Amyloid PET standardized uptake value ratio (SUVR) composite at 18 months for brain amyloid levels as measured
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog$_{14}$, CDR, MMSE, ISLT, CBB, and FAQ

### 9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose exploratory efficacy measurement. (revised per Amendment 05)
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

### 9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The number of randomized subjects enrolled at each site will be summarized by treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: The number (percent) of randomized and treated subjects who completed the study and who withdrew from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and withdrew from the study. The primary reasons for discontinuation from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

Completion of Study Treatment: The number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for discontinuation from the study drug are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, inadequate therapeutic response, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

#### 9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized by treatment group using descriptive statistics. Continuous demographic and baseline variables include age, MMSE and FAQ; categorical variables include sex, age group (≤65 years, age >65 years), race, ethnicity, *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal AD or mild to moderate AD). (revised per Amendment 01)

#### 9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014 or higher). (revised per Amendment 04) The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up period will also be recorded.

#### 9.7.1.6 Efficacy and Biomarker Analyses (revised per Amendment 05)

##### 9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

There is no primary efficacy endpoint. (revised per Amendment 05)

##### 9.7.1.6.2 SECONDARY EFFICACY ANALYSES

An mixed-effects model with repeated measures (MMRM) will be used to analyze the following secondary endpoint:

- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) from 4 weeks and up to 18 months. Data from early discontinuations will also be included. (revised per Amendment 05)

##### 9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

(revised per Amendments 01, 02, 04, and 05)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months. Data from early discontinuations will also be included. (revised per Amendment 04)
- Change from baseline in CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Change from baseline in plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during post-treatment follow-up
- Change from baseline in CSF amyloid and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment (revised per Amendment 06)
- Change from baseline in total hippocampal atrophy at 12 and 18 months as measured by vMRI
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and 18 months as measured by vMRI
- Change from baseline in Amyloid PET SUVR composite at 18 months for brain amyloid levels

The following efficacy endpoints will be summarized using descriptive statistics:

- Change from baseline in the clinical assessments: ADAS-cog$_{14}$, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months

The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

#### 9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

##### 9.7.1.7.1 PHARMACOKINETIC ANALYSES

The PK Analysis Set will be used for E2609 concentration listings and for summaries of E2609 concentrations in plasma and CSF by dose and day. E2609 metabolite PK data may also be listed and summarized. (revised per Amendment 04)

A population PK approach will be used to characterize the plasma PK of E2609. For this approach, plasma PK data from this study will be pooled with relevant data from Phase 1 studies. As appropriate, the effect of covariates on the PK of E2609 will be evaluated. The PK model will be parameterized for oral clearance (CL/F) and apparent volume of distribution (Vz/F) for E2609. Derived exposure parameters such as steady state area under the concentration time curve (AUC) and average concentration ($C_{avg}$) of E2609 and other derived parameters will be calculated from the model using the individual estimates parameterized for oral clearance and dosing history. (revised per Amendment 04)

##### 9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Pharmacodynamic, PGx, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate statistical analysis plan. Please also refer to Appendix 3.

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). The percentage change from baseline in CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months of treatment will be analyzed and presented graphically. (revised per Amendment 05) Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status. (revised per Amendment 04)

Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels, amyloid load on PET, vMRI, and E2609 dose, plasma, and CSF exposure will be initially explored graphically and any emergent relationship will be explored through population PK/PD modeling. The PK/PD relationship between plasma PK parameters with other biomarkers may also be explored using similar methods. (revised per Amendment 04)

The relationship between plasma and CSF exposure to E2609 and the clinical efficacy scales (eg, MMSE, CDR) will be explored graphically. Additionally, the relationship between plasma exposures of E2609 and select lymphocyte parameters will be explored graphically, and any emergent relationship will be explored using population-based modeling methods. (revised per Amendment 04)

Exposure-safety analyses may also be conducted.

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. The genomic DNA samples may also be stored and used as described in Section 9.7.1.7.2. Details of PGx testing may be provided and reported separately.

#### 9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements, and cognitive decline assessment such as CBB will be summarized by treatment group using descriptive statistics. (revised per Amendment 05)

##### 9.7.1.8.1 Extent of Exposure

The extent of exposure to study drug will be summarized as cumulative extent of exposure in 3-month intervals. The cumulative number and percent of subjects will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as continuous variable as well as categorical variable in 3-month intervals and the number and percent of subjects will be presented by treatment group.

##### 9.7.1.8.2 Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities

(MedDRA). Adverse events will be coded to the MedDRA (Version 17.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and preferred term. A subject will be counted only once within an SOC and preferred term, even if the subject experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and preferred term. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

Adverse events will be summarized by the following subgroups: *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal or mild to moderate AD). (revised per Amendment 01)

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

#### 9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

Lymphocyte subsets measured (including but not limited to CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages] and regulatory T cells) will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose.

Serum IgG, IgM, and IgA will be measured and summarized in the same manner as other laboratory parameters.

#### 9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

#### 9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to the end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 msec
- QTc interval >480 msec
- QTc interval >500 msec

Change from baseline in QTc interval:

- QTc interval increases from baseline >30 msec
- QTc interval increases from baseline >60 msec

#### 9.7.1.8.6 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include CBB (Section 9.7.1.6). (revised per Amendment 05)

### 9.7.2 Determination of Sample Size

A total of 15 subjects per dose group is deemed sufficient to derive adequate safety and PK/PD data to aid in the selection of appropriate doses and the design of the Phase 3 studies that may be planned subsequently. (revised per Amendment 05)

### 9.7.3 Interim Analysis

In order to make decisions about the remainder of the study as well as the full E2609 clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. Investigators, other clinical site staff, subjects, caregivers/informants, and study team will remain blinded to study treatment. (revised per Amendments 03 and 05)

An interim safety analysis will also be conducted when all subjects have completed 12 weeks of treatment (or discontinue study drug early). (revised per Amendments 01, 03, 04, and 05)

### 9.7.4 Other Statistical/Analytical Issues

**Stratification** (revised per Amendment 01)

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

### 9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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(revised per Amendment 01)

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# 11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

## 11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

## 11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

## 11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

## 11.4 Recording of Data

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document, except when a section of the eCRF itself is used as the source document. Any correction to entries made on the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each eCRF. The investigator will report the eCRFs to the sponsor and retain a copy of the eCRFs.

## 11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents.

## 11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

## 11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

## 11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

## 11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

## 11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or CTA executed between the institution/investigator and the sponsor/CRO.

## 11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

## 11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

# 12 APPENDICES

## Appendix 1 Sponsor's Grading for Laboratory Values

(revised per Amendment 01)

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **BLOOD/BONE MARROW** | | | | |
| Hemoglobin (conversion from g/dL×0.6206) | **Female** (ULN=15.9 g/dL)<br><11.1 – 10.0 g/dL<br><111 – 100 g/L<br><6.9 – 6.2 mmol/L<br>**Male** (ULN=17.7 g/dL)<br><12.6 – 10.0 g/dL<br><126 – 100 g/L<br><7.8 – 6.2 mmol/L | <10.0 – 8.0 g/dL<br><100 – 80 g/L<br><6.2 – 4.9 mmol/L | <8.0 g/dL<br><80 g/L<br><4.9 mmol/L;<br>transfusion indicated | life-threatening consequences; urgent intervention indicated |
| Leukocytes (total white blood cell) | <3.40 – 3.0×$10^9$/L<br><3.40 $10^3$/uL – 3000/$mm^3$<br>(ULN=10.80 $10^3$/μL) | <3.0 – 2.0×$10^9$/L<br><3000 – 2000/$mm^3$ | <2.0 – 1.0×$10^9$/L<br><2000 – 1000/$mm^3$ | <1.0×$10^9$/L<br><1000/$mm^3$ |
| Lymphocytes | not applicable | <700 – 500/$mm^3$<br><0.7 – 0.5×$10^9$/L | <500 – 200/$mm^3$<br><0.5 – 0.2×$10^9$/L | <200/$mm^3$<br><0.2×$10^9$/L |
| Neutrophils | not applicable | <1.4 – 1.0×$10^9$/L<br><1400 – 1000/$mm^3$ | <1.0 – 0.5×$10^9$/L<br><1000 – 500/$mm^3$ | <0.5×$10^9$/L<br><500/$mm^3$ |
| Platelets | <155 – 75.0×$10^9$/L<br><155 $10^3$/uL – 75,000/$mm^3$<br>(ULN=379 $10^3$/μL) | <75.0 – 50.0×$10^9$/L<br><75,000 – 50,000/$mm^3$ | <50.0 – 25.0×$10^9$/L<br><50,000 – 25,000/$mm^3$ | <25.0×$10^9$/L<br><25,000/$mm^3$ |
| **METABOLIC/LABORATORY** | | | | |
| Albumin, serum- low (hypoalbuminemia) | **2 - 59 years** (ULN=5.5 g/dL)<br><3.5 – 3 g/dL<br><35 – 30 g/L<br>**59 -69 years** (LLN-ULN)<br><3.6 g/dL – 3 g/dL<br>**69 -79 years** (LLN-ULN)<br><3.5 g/dL – 3g/dL<br>**79 -89 years** (LLN-ULN)<br><3.5g/dL – 3g/dL | <3 – 2 g/dL<br><30 – 20 g/L | <2 g/dL<br><20 g/L | life-threatening consequences; urgent intervention indicated |
| Alkaline phosphatase | **Female:**<br>**18 -19 years**<br>>101 – 3.0×101<br>**19 -61 years**<br>ULN=107<br>**61 -71 years**<br>ULN=112<br>**71 -150 years**<br>ULN=108<br>**Male**<br>**18 -19 years**<br>>127 – 3.0×127<br>**19 -61 years**<br>ULN=102<br>**61 -71 years**<br>ULN=103<br>**71 -150 years**<br>ULN=105 | >3.0 – 5.0×ULN<br>See previous column for ULN values | >5.0 – 20.0×ULN<br>See previous column for ULN values | >20.0×ULN<br>See previous column for ULN values |
| Alanine aminotransferase | **Female:**<br>>32 – 3.0×32 | **Female:**<br>>3.0 – 5.0×32 | **Female:**<br>>5.0 – 20.0×32 | **Female:**<br>>20.0×32 |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| | **Male:**<br>>44 – 3.0 x 44 | **Male**<br>>3.0 – 5.0×44 | **Male:**<br>>5.0 – 20.0×44 | **Male:**<br>>20.0×44 |
| Aspartate aminotransferase | >40 – 3.0×40 | >3.0 – 5.0×40 | >5.0 – 20.0×40 | >20.0×40 |
| Bilirubin (hyperbilirubinemia) | >1.2 – 1.5×1.2 | >1.5 – 3.0×1.2 | >3.0 – 10.0×1.2 | >10.0×1.2 |
| Calcium, serum-low (hypocalcemia) (conversion to mmol×0.25) | <8.5 – 8.0 mg/dL<br><2.13 – 2.0 mmol/L | <8.0 – 7.0 mg/dL<br><2.0 – 1.75 mmol/L | <7.0 – 6.0 mg/dL<br><1.75 – 1.5 mmol/L | <6.0 mg/dL<br><1.5 mmol/L |
| Calcium, serum-high (hypercalcemia) | >10.6 – 11.5 mg/dL<br>>2.65 – 2.9 mmol/L | >11.5 – 12.5 mg/dL<br>>2.9 – 3.1 mmol/L | >12.5 – 13.5 mg/dL<br>>3.1 – 3.4 mmol/L | >13.5 mg/dL<br>>3.4 mmol/L |
| Cholesterol, serum-high (hypercholesterolemia) (conversion to mmol/L ×0.02586) | **0 -19 years**<br>>169 – 300 mg/dL<br>>4.37 – 7.75 mmol/L<br>**19 -150 years**<br>>199 – 300 mg/dL<br>>5.15 – 7.75 mmol/L | >300 – 400 mg/dL<br>>7.75 – 10.34 mmol/L | >400 – 500 mg/dL<br>>10.34 – 12.92 mmol/L | >500 mg/dL<br>>12.92 mmol/L |
| Creatinine | **Female**<br>>1.00 mg/dL – 1.5×1.00<br>**Male**<br>>1.27 mg/dL – 1.5×1.27 | **Female**<br>>1.5 – 3.0×1.00<br>**Male**<br>>1.5 mg/dL – 3.0×1.27 | **Female**<br>>3.0 – 6.0×1.00<br>**Male**<br>>3.0 mg/dL – 6.0 ×1.27 | **Female**<br>>6.0×1.00<br>**Male**<br>>6.0×1.27 |
| Gamma glutamyl transpeptidase | **Female**<br>>60 IU/L – 3.0×60<br>**Male**<br>>65 IU/L – 3.0×65 | **Female**<br>>3.0 – 5.0×60<br>**Male**<br>>3.0 – 5.0×65 | **Female**<br>>5.0 – 20.0×60<br>**Male**<br>>5.0 – 20.0×65 | **Female**<br>>20.0×60<br>**Male**<br>>20.0×65 |
| Glucose, serum-high (hyperglycemia) (conversion to mmol/L ×0.0555) | **Fasting glucose value**<br>>99 – 160 mg/dL<br>>5.5 – 8.9 mmol/L | **Fasting glucose value**<br>>160 – 250 mg/dL<br>>8.9 – 13.9 mmol/L | >250 – 500 mg/dL;<br>>13.9 – 27.8 mmol/L;<br>hospitalization indicated | >500 mg/dL;<br>>27.8 mmol/L;<br>life-threatening consequences |
| Glucose, serum-low (hypoglycemia) | <65 – 55 mg/dL<br><3.6 – 3.0 mmol/L | <55 – 40 mg/dL<br><3.0 – 2.2 mmol/L | <40 – 30 mg/dL<br><2.2 – 1.7 mmol/L | <30 mg/dL<br><1.7 mmol/L<br>life-threatening consequences;<br>seizures |
| Phosphate, serum-low (hypophosphatemia) (conversion to mmol/L ×0.323) | not applicable | <2.5 – 2.0 mg/dL<br><0.8 – 0.6 mmol/L | <2.0 – 1.0 mg/dL<br><0.6 – 0.3 mmol/L | <1.0 mg/dL<br><0.3 mmol/L<br>life-threatening consequences |
| Potassium, serum-high (hyperkalemia) | not applicable | >5.5 – 6.0 mmol/L | >6.0 – 7.0 mmol/L<br>hospitalization indicated | >7.0 mmol/L<br>life-threatening consequences |
| Potassium, serum-low (hypokalemia) | <3.5 mEq/L – 3.0 mmol/L | <LLN – 3.0 mmol/L;<br>symptomatic; intervention indicated | <3.0 – 2.5 mmol/L<br>hospitalization indicated | <2.5 mmol/L<br>life-threatening consequences |
| Sodium, serum-high (hypernatremia) | >144 mEq/L – 150 mmol/L | >150 – 155 mmol/L | >155 – 160 mmol/L<br>hospitalization indicated | >160 mmol/L<br>life-threatening consequences |
| Sodium, serum-low (hyponatremia) | <134 mEq/L – 130 mmol/L | Not applicable | <130 – 120 mmol/L | <120 mmol/L<br>life-threatening consequences |
| Triglyceride, serum-high (hypertriglyceridemia) | 150 – 300 mg/dL<br>1.71 – 3.42 mmol/L | >300 – 500 mg/dL<br>>3.42 – 5.7 mmol/L | >500 – 1000 mg/dL<br>>5.7 – 11.4 mmol/L | >1000 mg/dL<br>>11.4 mmol/L<br>life-threatening consequences |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Uric acid, serum-high (hyperuricemia) | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | Not applicable | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | >10 mg/dL<br>>0.59 mmol/L<br>life-threatening consequences |

LLN = lower limit of normal, ULN = upper limit of normal.

# Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1 through Listing 5. Medications permitted with restrictions are listed in Listing 6 through Listing 8. (revised per Amendment 04) **These may not be all-inclusive listings.** Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-202 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 8 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

## Prohibited Prior/Concomitant Medications

### Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Prohibited from 14 days (or 5 half-lives, whichever is longer) before Randomization until after the last treatment visit** | | |
| **Anti-arrhythmic/ abnormal heart rhythm** | | |
| Amiodarone | Cordarone; Pacerone | Incidence in females greater than males, Torsades de Pointes risk regarded as low |
| Disopyramide | Norpace | Incidence in females greater than males |
| Dofetillide | Tikosyn | |
| Ibutilide | Corvert | Incidence in females greater than males |
| Procainamide | Pronestyl; Procan | |
| Quinidine | Cardioquin; Quinaglute | Incidence in females greater than males |
| Sotalol | Betapace | Incidence in females greater than males |
| **Antihistamine/ allergic rhinitis** | | |
| Astemizole | Hismanal | No longer available in United States |
| Terfenadine | Seldane | No longer available in United States |
| **Anti-anginal/ heart pain** | | |
| Bepridil | Vascor | Incidence in females greater than males |
| **Antibiotic/ bacterial infection** | | |
| Clarithromycin | Biaxin | |
| Moxifloxacin | Avelox | |
| Sparfloxadin | Zagam | |
| **Listing 1 continued** | | |
| **Antimalarial/ malaria infection** | | |
| Chloroquine | Aralen | |
| Halofantrine | Halfan | Incidence in females greater than males |
| **Antipsychotic/ anti-emetic/ schizophrenia/ nausea** | | |
| Chloropromazine | Thorazine | |
| **Gastrointestinal stimulant/ heartburn** | | |
| Cisapride | Propulsid | |

## Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Antinausea/ nausea** | | |
| Domperidone | Motillum | Not available in the United States |
| **Sedative; antinausea/ anesthesia adjunct, nausea** | | |
| Droperidol | Inapsine | |
| **Antibiotic; gastrointestinal stimulant/ bacterial infection; increase gastrointestinal motility** | | |
| Erythromycin | Erythrocin; E.E.S. | Incidence in females greater than males |
| **Antipsychotic/ schizophrenia** | | |
| Haloperidol | Haldol | When given intravenously or at higher than recommended doses, risk of sudden death, QT prolongation, and torsades increases |
| Mesoridazine | Serentil | |
| Thioridazine | Mellaril | |
| **Opiate agonist/ pain control, narcotic dependence** | | |
| Levomethadyl | Orlaam | |
| Methadone | Methadose; Dolophine | Incidence in females greater than males |
| **Anti-infective/ pneumocystis pneumonia** | | |
| Pentamidine | Pentam; NebuPent | Incidence in females greater than males |
| **Antipsychotic/ Tourette's tics** | | |
| Pimozide | Orap | Incidence in females greater than males |
| **Antilipemic/ hypercholesterolemia** | | |
| Probucol | Lorelco | No longer available in United States |
| **Anticancer** | | |
| Arsenic trioxide | Trisenox | Used for leukemia |
| Vandetanib | Zactima | Used for thyroid cancer |

Note: This list is not exhaustive.

QTc = Corrected QT interval.

## Listing 2 Prohibited Medications Within 5 Half-lives or 60 days, Whichever is Longer, Before Randomization and Until after the Last Treatment Visit

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Systemic Immunosuppressants[a,b] and Immunomodulatory therapy** | |
| Azathioprine | Azasan, Imur |
| Ciclosporine | Gengraf, Neoral |
| Dexamethasone | Decadron, Dexasone, Diodex, Hexadrol, Maxidex |
| Fingolimod | Gilenya |
| Methotrexate | Trexall |
| Methylprednisolone | Medrol, Meprolone |
| Mycophenolate | CellCept, Myfortic |
| Prednisolone | Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS |

Note: This list is not exhaustive.

a: Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

b: During the treatment period of the study, short term (not more than 14 days) use of steroids up to the equivalent of prednisolone 40 mg OD is permitted after discussion with the Medical Monitor. Dosing with study drug should be suspended from the time steroid treatment is started. Complete blood count and lymphocyte subsets should be determined prior to starting steroid treatment and continue to be monitored weekly. Study drug may be resumed after discussion with the Medical Monitor when the following conditions are met: (1) treatment with steroids has been completed for at least 1 week; (2) total lymphocytes not <LLN; (3) no lymphocyte subsets are below the discontinuation threshold; (4) the investigator considers that the medical condition which required treatment with steroids has improved or resolved. Weekly testing of lymphocyte subset counts and CBC with differentials is required for 4 weeks following resumption of study drug administration. (revised per Amendment 04)

## Listing 3 Prohibited Medications Within 6 Months Before Randomization

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Immunoglobulin therapy** | |
| Adalimumab | Humira |
| Bevacizumab | Avastin |
| Efalizumab | Raptiva |
| Etanercept | Enbrel |
| Immune globulin IV, IVIG, IGIV | Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S |
| Infliximab | Remicade |
| Omalizumab | Xolair |
| Ranibizumab | Lucentis |
| Other monoclonal antibodies not listed here | |

Note: This list is not exhaustive.

### Listing 4 Prohibited Live Vaccines Within 3 Months Before Randomization Until after the Last Treatment Visit (this does not apply to non-live/inactivated vaccines)

| **Bacterial vaccines** | **Viral vaccines** |
|---|---|
| Bacillus Calmette-Guérin vaccine against tuberculosis | Measles vaccination |
| Cholera vaccination (oral) | Rubella vaccination |
| | Oral polio vaccination (Sabin) |
| | Yellow fever vaccination |
| | Varicella (chickenpox) vaccination |
| | Rotavirus vaccination |
| | Japanese encephalitis vaccination |
| | Live attenuated influenza vaccine (FluMist, Fluenz) |
| Typhoid vaccination (oral) | Mumps vaccination |

Note: This list is not exhaustive

## Listing 5 Strong CYP3A4 Inhibitors Prohibited Within 5 Half-Lives or 14 Days (Whichever Is Longer) Before Randomization Until After the Last Treatment Visit

| Generic name | Brand name(s) |
|---|---|
| boceprevir | Victrelis |
| clarithromycin | Clarithromycin, clarithromycin extended release, Prevpac |
| cobicistat | Tybost, Stribild, |
| conivaptan | Vaprisol |
| danoprevir | |
| elvitegravir | Vitekta, Stribild |
| indinavir | Crixivan |
| itraconazole | Sporanoz, Onmel |
| ketoconazole | Xolegel, Nizoral, Ketodan |
| lopinavir | Kaletra |
| nefazodone | Serzone |
| nelfinavir | Viracept |
| posaconazole | Noxafil |
| ritonavir | Norvir, Kaletra |
| saquinavir | Invirase, Fortovase |
| telaprevir | Incivek |
| telithromycin | Ketek |
| tipranavir | Aptivus |
| troleandomycin | Triocetin |
| voriconazole | Vfend, Voriconazole |

Note: This list is not exhaustive

## Permitted Prior/Concomitant Medications

### Listing 6 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Baseline Cognitive Assessments at Visit 2 and Remain on the Same Stable Dose from Baseline to Final Follow-Up Visit

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Cognitive Enhancers** | |
| Donepezil | Aricept |
| Galantamine | Reminyl |
| Memantine | Namenda |
| Rivastigmine | Exelon |

Note: This list is not exhaustive.

## Listing 7 Permitted Medications Used on PRN Basis Which are Not to be Used Within 72 Hours before Cognitive Testing

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Opiates** | |
| Morphine | Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol |
| **Opiate Agonists** | |
| Codeine | Codeine |
| Fentanyl | Actiq, Duragesic, Fentora, Onsolis, Sublimaze |
| Meperidine | Demerol, Meperitab |
| Oxycodone | Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol |
| Other opioids or opioid agonists which are used on PRN basis | |
| **Benzodiazepines and sedatives** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Amitriptyline | (various) |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Dothiepin | (various) |
| Estazolam | ProSom |
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |
| Lorazepam | Ativan |
| Midazolam | Versed |
| Olanzapine | Zyprexa |
| Promethazine | Phenergan; others |
| Ramelteon | Rozerem |
| Risperidone | Risperdal |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zolpidem | Ambien; others |
| Zopiclone | (various) |
| Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives | |

Note: This list is not exhaustive

## Listing 7 Permitted Medications Used on PRN Basis Which are Not to be Used Within 72 Hours before Cognitive Testing

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|

PRN = Pro re nata

## Listing 8 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| If to be used on a PRN basis see Listing 7. If to be used chronically, subjects must be on a stable dose for ≥4 weeks before Baseline. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks. | |
| **Antidepressants** | |
| Amitriptyline hydrochloride | Elavil |
| Amoxapine | Amoxapine |
| Bupropion | Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin |
| Citalopram | Celexa |
| Clomipramine hydrochloride | Anafranil |
| Desipramine hydrochloride | Norpramin |
| Desvenlafaxine | Pristiq |
| Doxepin hydrochloride | Prudoxin, Silenor, Sinequan, Zonalon |
| Duloxetine | Cymbalta |
| Escitalopram | Lexapro |
| Fluoxetine | Prozac, Sarafem, Selfemra |
| Fluvoxamine | Luvox |
| Imipramine hydrochloride | Tofranil |
| Isocarboxazid | Marplan |
| Maprotiline hydrochloride | Ludiomil |
| Mirtazapine | Remeron Soltab |
| Nortriptyline hydrochloride | Aventyl, Pamelor |
| Paroxetine | Paxil, Pexeva |
| Phenelzine | Nardil |
| Protriptyline hydrochloride | Vivactil |
| Rasagiline | Azilect |
| Selegiline | EMSAM |
| Sertraline | Sertaraline, Zoloft |
| Tranylcypromine | Parnate |
| Trazodone hydrochloride | Desyrel, Oleptro |
| Trimipramine maleate | Surmontil |
| Venlafaxine hydrochloride | Effexor |

## Listing 8 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Mood Stabilizers (Listing 8 continued)** | |
| Carbamazepine | Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR |
| Lamotrigine | Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR |
| Valproic acid | Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate |
| **Antipsychotics** | |
| Acetophenazine | Tindal |
| Aripiprazole | Abilify |
| Asenapine | Saphris |
| Olanzapine | Zyprexa |
| Chlorpromazine | Thorazine |
| Haloperidol | Haloperidol, Haldol |
| Clozapine | Clozaril, Fazaclo |
| Fluphenazine | Prolixin |
| L-Methylfolate | Deplin, L-Methylfolate Calcium |
| Loxapine | Loxitane |
| Mesoridazine | Serentil |
| Perphenazine | Trilafon |
| Quetiapine | Seroquel |
| Risperidone | Risperdal |
| Thioridazine | Mellaril |
| Thiothixene | Navane |
| Trifluoperazine | Stelazine |
| **Benzodiazepines** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Estazolam | ProSom |

## Listing 8 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |
| Lorazepam | Ativan |
| Midazolam | Versed |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zopiclone | Imovane, Zimovane |
| Zopidem | Ambien, Ambien CR, Intermezzo, Stilnox, Stilnoct, Sublinox, Hypnogen, Zolsana |

Note: This list is not exhaustive.

PRN = Pro re nata

# Appendix 3 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

## Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

## Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In

this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

### Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

### Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed

scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

# Appendix 4 AEs Indicating Signals of Possible Drug Abuse Potential

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| 1 | **Euphoric mood** | Euphoric mood |
| | | Euphoria |
| | | Euphoric |
| | | Exaggerated well-being |
| | | Excitement excessive |
| | | Feeling high |
| | | Felt high |
| | | High |
| | | High feeling |
| | | Laughter |
| 2 | **Elevated mood** | Elevated mood |
| | | Mood elevated |
| | | Elation |
| 3 | **Feeling abnormal** | Feeling abnormal |
| | | Cotton wool in head |
| | | Feeling dazed |
| | | Feeling floating |
| | | Feeling strange |
| | | Feeling weightless |
| | | Felt like a zombie |
| | | Floating feeling |
| | | Foggy feeling in head |
| | | Funny episode |
| | | Fuzzy |
| | | Fuzzy head |
| | | Muzzy head |
| | | Spaced out |
| | | Unstable feeling |
| | | Weird feeling |
| | | Spacey |
| 4 | **Feeling drunk** | Feeling drunk |
| | | Drunkenness feeling of |
| | | Drunk-like effect |
| | | Intoxicated |
| | | Stoned |
| | | Drugged |
| 5 | **Feeling of relaxation** | Feeling of relaxation |
| | | Feeling relaxed |
| | | Relaxation |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Relaxed |
| | | Increased well-being |
| | | Excessive happiness |
| **6** | **Thinking abnormal** | Thinking abnormal |
| | | Abnormal thinking |
| | | Thinking irrational |
| | | Thinking disturbance |
| | | Thought blocking |
| | | Wandering thoughts |
| **7** | **Hallucination** | Hallucination |
| | | Illusions |
| | | Flashbacks |
| | | Floating |
| | | Rush |
| | | Feeling addicted |
| **8** | **Inappropriate affect** | Elation inappropriate |
| | | Exhilaration inappropriate |
| | | Feeling happy inappropriately |
| | | Inappropriate affect |
| | | Inappropriate elation |
| | | Inappropriate laughter |
| | | Inappropriate mood elevation |
| **9** | **Mood disorders and disturbances** | Mental disturbance |
| | | Depersonalisation |
| | | Psychomotor stimulation |
| | | Mood disorders |
| | | Emotional and mood disturbances |
| | | Delirium |
| | | Delirious |
| | | Mood altered |
| | | Mood alterations |
| | | Mood instability |
| | | Mood swings |
| | | Emotional lability |
| | | Emotional disorder |
| | | Emotional distress |
| | | Personality disorder |
| | | Impatience |
| | | Abnormal behavior |
| | | Delusional disorder |
| | | Irritability |
| **10** | **Drug tolerance** | Drug tolerance |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Habituation |
| | | Drug withdrawal syndrome |
| | | Substance-related disorders |
| **11** | **Psychosis** | Psychosis |
| | | Psychotic episode or disorder |
| **12** | **Dissociative State** | Dissociation |
| | | Disconnected |
| | | Derealisation |
| | | Depersonalisation |
| | | Detached |
| | | Sensation of distance from one's environment |
| | | Loss of a sense of personal identity |

# Appendix 5 Eisai Lymphocyte Subset Criteria for Study E2609-G000-202: Justification for a Population-Adjusted Approach

**Introduction:**

The Eisai clinical study, E2609-G000-202, requires the analysis of absolute numbers of various functional subsets of circulating lymphocytes. These are distinguished by identification of various complementary differentiation (CD) markers on the cell surface using fluorescent-labeled antibody reagents and flow cytometry. Current enumeration of certain lymphocyte subsets form part of the immunologically based eligibility criteria for study enrollment, as well as being monitored for safety for enrolled and treatment randomized subjects. The Trucount™ M (Becton, Dickinson and Company [BD], BD Biosciences, San Jose, CA) antibody reagents used for the lymphocyte subset eligibility criteria, provides readouts for both absolute (BD Trucount tubes) and percentage of lymphocyte subsets, and includes the following CD markers: CD3 (T cells), CD4 (T helper cells), CD8 (cytotoxic T cells), CD16/56 (natural killer cells), CD14 (macrophages), and CD19 (B cells).

Trucount lymphocyte subset reference ranges provided by the reagent manufacturer (BD) for both absolute and percentages were established for clinical use as an in vitro diagnostic using standardized reference interval methodology. These LLN for the various lymphocyte subsets are currently being used by the central laboratory for Eisai Study E2609-G000-202 to determine eligibility of screened subjects and as part of safety assessments during post-randomization visits. The eligibility criterion excludes subjects with absolute counts of T and B cell markers (CD4, CD8, and CD19 respectively) less than the reference range lower limit of normal (<LLN) at Screening or Baseline.

**Need to assign age appropriate reference ranges:**

Reference ranges established by the vendor according to working group guidance[(3)] may not be representative of different subgroup analyses (eg, ancestry, disease state, age, gender, etc.), and therefore interval adjustment may be required depending on the subpopulation of interest. The working group guidance for reference intervals (CLSI, 2010[(4)]) recommends examining data to determine if >10% of subjects are outliers (ie, more than 10% < LLN), and if so, to initiate development of subgroup-appropriate intervals by analyzing data from the literature or internal studies representing the reference population [a minimum of 120 observations recommended by the guidance.[(3)]]

Data from the ongoing Study E2609-G000-202 has been examined and greater than 10% of the study population screening samples fall below the manufacturer recommended LLN for the key lymphocyte subsets. The population for Study E2609-G000-202 are patients aged 50 to 85 years old inclusive with Mild Cognitive Impairment due to AD or with Mild to Moderate dementia due to AD. Lymphocyte subset data from a data cut of 93 screened

subjects was analyzed and showed that both CD8 and CD4 had greater than 10% of the subjects with results <LLN (26.9%, <220 cells/$mm^3$ and 13%, <404 cells/$mm^3$, respectively); CD19 had approximately 10% of the subjects with results <LLN (9.7%, <80 cells/$mm^3$).

To further determine if the outlier data observations from the ongoing Study E2609-G000-202 were associated with disease status or age, lymphocyte subset data from additional Eisai studies that included healthy elderly subjects or patients diagnosed with MCI or mild/moderate AD were examined. The individuals from all 3 studies included the same 50-to 85-year-old age range as the current E2609-G000-202 study. The studies evaluated include: (1) Study E2609-A001-002 treatment study (n=50 healthy elderly); (2) Lymphocyte subset pilot study in healthy elderly [n=30]; and (3) Lymphocyte subset pilot study in AD/MCI [n=31]. Screening or baseline sample from all 4 studies had >10% of the CD8 absolute counts below reference LLN, 2 out of 4 had >10% of the CD19 absolute counts below reference LLN and 1 out of 4 had >10% of the CD4 absolute counts out of reference LLN [Table 10, Table 11, and Table 12]. The data suggests that the reference values of LLN for CD4, CD8, and CD19 subsets are not a disease-associated observation but are related to the age of the study population being evaluated.

In addition to the Eisai study data, age related decline in lymphocyte subsets has been described in the literature Yan et.al.[1][2] Analysis was performed using flow cytometry on peripheral blood leukocytes using healthy subjects across the 3rd and 10th decades of life. The results from the Yan study (n=80; 37 males, 43 females) demonstrated that with advancing age there was a significant decline in the percentage of lymphocytes, specifically naive T cells [CD3 *P*=0.03], cytotoxic T cells [CD8 *P*=0.08] and activated B cells [CD20/CD69 *P*=0.03] with certain subsets demonstrating even greater decline in males.[1] The age associated changes in immune capabilities, termed “immunosenescence”, which include degenerative changes in the lymph nodes, effects on lymphocyte subsets and changes in adaptive immunity may underlie the increased risk of infection and cancer and decreased immune function in the elderly. This, along with the data from the four Eisai studies described earlier, support the readjustment of the LLNs for the CD reference ranges used for eligibility in Study E2609-G000-202 such that they are better suited to the older patient population enrolling in this study which is thought to be representative of the wider patient population.

**Determining the new LLN criteria:**

The recommended method for establishing reference intervals is the nonparametric approach where the underlying distribution of the data does not matter. The values received from the data (a minimum of 120 observations representing the subgroup population of interest is recommended) are rank ordered and can be used to evaluate the comparative reference interval.[3]

When data from the 4 Eisai studies are put in rank order (see Table 10, Table 11, and Table 12), and a 10% cut value is applied to each of the 3 CD markers of interest the following age-adjusted LLN values are generated:

**Table 9 Summary of CD4, CD8, and CD19 LLNs and Age-Adjusted LLNs**

| Lymphocyte Subset | Current LLN | Age-adjusted LLN |
|---|---|---|
| CD4 absolute count | 404 cells/$mm^3$ | 396 cells/$mm^3$ |
| CD8 absolute count | 220 cells/$mm^3$ | 157 cells/$mm^3$ |
| CD19 absolute count | 80 cells/$mm^3$ | 74 cells/$mm^3$ |

**Table 10 Summary of CD Counts (Parameter: CD19)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 30 | 203 |
| Mean | 213.47 | 198.49 | 159.20 | 172.77 | 192.57 |
| Median | 189.66 | 163.00 | 118.50 | 159.50 | 164.86 |
| 5th percentile | 84.81 | 59.00 | 38.00 | 69.00 | 59.00 |
| 10th percentile | 102.26 | 81.00 | 42.00 | 70.50 | 74.00 |
| 25th percentile | 139.66 | 104.00 | 75.00 | 100.00 | 104.58 |
| 75th percentile | 261.51 | 225.00 | 225.00 | 246.00 | 246.00 |
| 95th percentile | 376.67 | 443.00 | 424.00 | 384.00 | 402.00 |
| Range | 66.19, 593.48 | 17.00, 1066.00 | 37.00, 455.00 | 39.00, 415.00 | 17.00, 1066.00 |

**Table 11 Summary of CD Counts (Parameter: CD8)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 31 | 204 |
| Mean | 362.72 | 352.18 | 324.63 | 427.74 | 362.20 |
| Median | 364.74 | 330.00 | 344.00 | 315.00 | 336.39 |
| 5th percentile | 115.02 | 138.00 | 86.00 | 100.00 | 115.02 |
| 10th percentile | 170.24 | 151.00 | 159.50 | 153.00 | 157.00 |
| 25th percentile | 253.37 | 213.00 | 204.00 | 217.00 | 230.00 |
| 75th percentile | 465.52 | 425.00 | 405.00 | 494.00 | 438.00 |
| 95th percentile | 614.57 | 716.00 | 557.00 | 988.00 | 702.00 |

**Table 11 Summary of CD Counts (Parameter: CD8)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| Range | 98.45, 702.50 | 37.00, 803.00 | 61.00, 702.00 | 54.00, 2255.00 | 37.00, 2255.00 |

**Table 12 Summary of CD Counts (Parameter: CD4)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 31 | 204 |
| Mean | 846.15 | 839.58 | 789.27 | 804.52 | 828.46 |
| Median | 836.94 | 805.00 | 777.50 | 771.00 | 791.50 |
| 5th percentile | 388.44 | 337.00 | 395.00 | 351.00 | 344.00 |
| 10th percentile | 479.55 | 361.00 | 490.00 | 427.00 | 396.00 |
| 25th percentile | 639.54 | 620.00 | 661.00 | 669.00 | 633.77 |
| 75th percentile | 1031.49 | 1078.00 | 924.00 | 1014.00 | 1039.50 |
| 95th percentile | 1315.55 | 1404.00 | 1124.00 | 1327.00 | 1347.00 |
| Range | 274.90, 1643.55 | 197.00, 1481.00 | 248.00, 1720.00 | 143.00, 1336.00 | 143.00, 1720.00 |

References:

1. Yan et al., Immunity and Ageing 2010 v. 7:4; The effect of ageing on human lymphocyte subsets: comparison of males and females.
2. Wikby et al., Biogerontology 2008 vol 9: 299; The immune risk profile is associated with age and gender: findings from three Swedish population studies of individuals 20-100 years of age.
3. Horowitz eJIFCC 2008 vol. 19 (2) Reference intervals: practical aspects).
4. Horowitz et al., CLSI Vol 28 no. 30 Clinical and Laboratory Standards Institute's (CLSI) newly revised document Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition (C28-A3), published in November 2010 EP28-AC3

# PROTOCOL SIGNATURE PAGE

(revised per Amendment 05)

**Study Protocol Number:** E2609-G000-202
**Study Protocol Title:** A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01 and 05)
**Investigational Product Name:** E2609
**IND Number:** 109308
**EudraCT Number:** 2014-002723-94

**SIGNATURES**
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# INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01 and 05) |
| **Investigational Product Name:** | E2609 |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

| Investigator | Signature | Date |
|---|---|---|

# REVISION HISTORY

**Revisions to Version 6.0**

**New version/date: Version 7.0 / 26 Sep 2016 (per Amendment 05)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Grammatical, typographical, and formatting changes | | Throughout |
| Remove Stage B from protocol. In line with this decision, the study objectives and endpoints have been modified and subjects who discontinue study drug early for any reason will no longer be required to complete efficacy visits after last dose of study drug. | This study will no longer be a Proof-of-Concept study. | Synopsis<br>• Study Protocol Title<br>• Investigators<br>• Sites<br>• Study Period and Phase of Development<br>• Objectives<br>• Study Design<br>• Early Discontinuation<br>• Number of Subjects<br>• Study Treatments<br>• Efficacy Assessments<br>• Safety Assessments<br>• Statistical Methods<br>• Study Endpoints<br>• Analysis Sets<br>• Efficacy and Biomarker Analyses<br>• Analysis for the Primary/Secondary/Exploratory Endpoints<br>• Pharmacokinetic Analyses<br>• Pharmacokinetic /Pharmacodynamic Analyses<br>• Interim Analyses<br>• Sample Size Rationale<br>Section 6<br>Section 7<br>Section 8<br>Section 8.3<br>Section 9.1<br>Section 9.2.1<br>Section 9.2.3<br>Section 9.2.4.4<br>Section 9.2.5 |

**Revisions to Version 6.0**

**New version/date: Version 7.0 / 26 Sep 2016 (per Amendment 05)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | | Section 9.3<br>Section 9.4.3<br>Section 9.4.4<br>Section 9.4.7<br>Section 9.2.5<br>Section 9.5.1.3.1<br>Section 9.5.1.4.2<br>Section 9.5.1.5.1<br>Section 9.5.2<br>Section 9.5.4.1<br>Section 9.5.5<br>Section 9.7<br>Section 10 |
| Updated Eisai contact information | Change in personnel and move to Building 100 | • Title Page<br>• Protocol Signature Page |

**Revisions to Version 5.0**

**New version/date: Version 6.0 / 29 Jun 2016 (per Amendment 04)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised number of investigational sites (from 40 to 35) | Feasibility | • Synopsis -<br>o Study Design<br>o Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Removed Exclusion Criterion No. 44 for male subjects regarding restrictions on child bearing | No longer a safety concern; E2609 has not shown a deleterious effect on sperm in preclinical reproductive toxicity studies. | • Synopsis:<br>o Exclusion Criteria<br>• Section 9.3.2 |
| Added option for subjects who provided a CSF sample prior to randomization but who declined the CSF sample collection after 4 weeks of dosing to provide a postdose CSF sample at any point in the study (ie, even after 4 weeks of dosing). | Reflects the added value of CSF data for the PK/PD secondary objective of this study. In addition, given that PK steady state is achieved within the 1st 2 weeks of initiation of dosing, data collected post Week 4 visit is still considered to be applicable in assessment of the steady state effect. | • Synopsis -<br>o Pharmacodynamic Assessments<br>• Section 5.3<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.5.1.3.3<br>• Section 9.5.1.4<br>• Table 6<br>• Table 7<br>• Table 8 |
| Revised details of restrictions to anticoagulant therapy and short-term steroid use revised/moved details regarding antiplatelet drugs to the main body of the protocol | To assist in subject recruitment and retention and considering that the strict restrictions were not necessary for subject safety | • Synopsis -<br>o Concomitant Drug/Therapy<br>• Section 9.4.7<br>• Appendix 2 |
| Removed the >33% decrease from baseline for CD4, CD8, and CD19 as a trigger for more frequent testing of flow cytometry and CBCs. Additional safety monitoring for CD4, CD8, CD19, and CBCs will only be based on the population adjusted LLNs for clinically asymptomatic subjects. | Experience to date has indicated significant variability within the normal range, both for increases and decreases. Absolute counts of lymphocyte subsets are more meaningful than percentage decreases for triggering more frequent monitoring. | • Section 9.3.3<br>• Table 1<br>• Table 2 |

**Revisions to Version 5.0**

**New version/date: Version 6.0 / 29 Jun 2016 (per Amendment 04)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Added option to temporarily suspend study drug for subjects who are clinically asymptomatic but who meet CD4, CD8, or CD19 discontinuation thresholds on 2 consecutive tests. Introduce rules for ability to re-start study drug (ie, rechallenge) in these subjects. Only 1 cycle of temporary suspension and rechallenge with study drug permitted for any individual subject. | To assist in subject retention and to gain knowledge on the behavior of lymphocyte subsets on rechallenge. | • Section 9.3.3<br>• Table 1<br>• Table 2 |
| Added extra blood draw times with focus on lymphocyte subsets, CBCs, and immunoglobulins during the 12-week safety follow-up for all subjects. | To increase frequency of key safety monitoring parameters in post-treatment follow-up period so as to assess immunological changes after completion of study drug | • Synopsis<br>o Study Design<br>o Safety Assessments<br>• Section 9.1.2.2<br>• Section 9.1.2.3<br>• Section 9.2.5<br>• Section 9.3.3<br>• Table 7<br>• Table 8<br>• Section 9.5.1.5.7<br>• Section 9.5.5 |
| Clarified that the Functional Assessment Questionnaire is to be administered to the informant/caregiver, and not the subject. | Clarification | • Synopsis<br>o Efficacy Assessments<br>• Section 9.5.1.3.1 |
| Added clarification that the Brief Smell Identification Test will be administered as part of the neurological examination | Clarification | • Synopsis<br>o Safety Assessments<br>o Interim Analyses<br>• Section 9.1.1.2<br>• Section 9.5.1.2.1<br>• Section 9.5.1.5.9<br>• Table 6<br>• Table 7 |

**Revisions to Version 5.0**

**New version/date: Version 6.0 / 29 Jun 2016 (per Amendment 04)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised number of randomized subjects in Stage A to n=60±20% | To allow for additional randomization based upon current number of subjects in screening at the time of amendment implementation | • Synopsis<br>  ○ Study Design<br>  ○ No. of Subjects<br>• Section 7<br>• Section 9.1<br>• Section 9.2.1<br>• Section 9.2.5<br>• Section 9.3<br>• Section 9.7.3 |
| Grammatical, typographical, and formatting corrections | Consistency | various |

**Revisions to Version 4.0**

**New version/date: Version 5.0, 06 Feb 2016 (per Amendment 03)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Add interim analyses of safety, and PK/PD data throughout Stage A | Decision making regarding the remainder of the study and the full E2609 clinical development program | • Synopsis –<br>o Exploratory Endpoint Analysis<br>o Interim Analysis<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.4.6<br>• Section 9.7.1.7.1 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Grammatical, typographical, and formatting changes | | Throughout |
| Mandatory nature of CSF collection in study changed to voluntary. This change impacts the timing and details of the PK/PD interim analyses. It also impacts the nature of the CSF-related objectives, which will now be identified as exploratory. | To increase rate of subject consent into the study | • Synopsis –<br>o Secondary Objectives<br>o Exploratory Objectives<br>o Study Design<br>o Exclusion Criterion No. 12<br>o Pharmacokinetic Assessments<br>o Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments<br>o Safety Assessments<br>o Secondary Endpoints<br>o Exploratory Endpoints<br>o Analysis for the Secondary Endpoints<br>o Analysis for the Exploratory Endpoints<br>• Section 5.3<br>• Section 8.2<br>• Section 8.3<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.2.5<br>• Section 9.3.2<br>• Section 9.4.6<br>• Section 9.5.1.3.3<br>• Section 9.5.1.4<br>• Section 9.5.1.5.12<br>• Section 9.7.1.1.2<br>• Section 9.7.1.1.3<br>• Section 9.7.1.6.2<br>• Section 9.7.1.6.3<br>• Appendix 2, Listing 2 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Extended the range of cognitive impairment in delayed recall that would be considered inclusionary for the study and removed the eligibility nature of the cognitive tests repeated at the Baseline Visit. | Original delayed recall aspect of inclusion criterion #1 was considered to be too restrictive and was unnecessarily screening out subjects with MCI/prodromal AD. The eligibility nature of the cognitive tests repeated at the Baseline Visit has been removed in order to simplify the requirements of the pretreatment period for the study. | • Synopsis –<br>  ○ Inclusion/ Exclusion Criteria<br>• Section 9.3.1<br>• Section 9.3.2 |
| Addition of historical amyloid PET scans for determination of eligibility for the study. Subjects with historical PET scans will not be part of the longitudinal PET analyses and therefore will not require a second PET scan at either Visit 18 or ED. | To provide the sites with greater operational flexibility and reduce subject burden. | • Synopsis –<br>  ○ Inclusion/Exclusion<br>  ○ Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments<br>• Section 9.1.1<br>• Section 9.2.4.3<br>• Section 9.3.1<br>• Section 9.5.2<br>• Table 6<br>• Table 7 |
| Added the need for safety laboratory tests to be repeated for subjects whose pre-treatment period is extended due to active infection. | To ensure that all baseline safety laboratory tests are repeated for subjects whose pretreatment period is extended. | • Synopsis –<br>  ○ Inclusion/Exclusion<br>• Section 9.3.2<br>• Section 9.5.2<br>• Table 6 |
| Clarified that exclusion criterion No. 22 (exclusion of subjects with CD4, CD8, or CD19 absolute counts below the LLN) applies to flow cytometry tests conducted at both the Screening and the Baseline Visits. Furthermore, LLNs that are adjusted for the subject population under study will be used. | It was not clear that Exclusion Criterion No. 22 applied to both the Screening and the Baseline Visits. The LLNs for CD4, CD8 and CD19 absolute counts require adjustment for the age of the patient population in this study. | • Synopsis –<br>  ○ Inclusion/ Exclusion Criteria<br>• Section 9.3.2 |
| Provided additional detail | Added to provide clarity | • Synopsis – |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| regarding scope of Exclusion Criterion No. 34 which excludes subjects with hypopigmentation conditions. | for the sites. | ○ Exclusion Criteria<br>• Section 9.3.2 |
| Revised number of clinical sites from 30 to 40 | For feasibility purposes | • Synopsis –<br>○ Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Relaxed the requirement for the cognitive assessments at Screening Visit 1 to be conducted in a certain order and revised the recommended order in which the assessments could be conducted. | To provide the sites with greater operational flexibility. | • Section 9.1.1<br>• Figure 2<br>• Section 9.5.1.3.1<br>• Section 9.5.2<br>• Table 6 |
| Clarify the duration for which the Safety magnetic resonance imaging (MRI) scan, the amyloid PET scan and the lumbar puncture (LP) collected CSF conducted at Screening are considered valid. | To provide sites with greater operational flexibility, particularly for re-screening of screen fail subjects. | • Section 9.1.1 |
| Clarify that for subjects meeting criteria for weekly monitoring of lymphocyte subsets, these can be accommodated within the scheduled clinic visits during the early stages of the treatment period of the study. | To provide operational clarity to the sites. | • Synopsis –<br>○ Exclusion Criteria<br>• Section 9.3.2<br>• Section 9.3.3<br>• Section 9.5.1.5.3 |
| Added the requirement for complete blood counts (CBC) with differentials to be performed whenever repeat or unscheduled flow cytometry tests are performed. | Such that CBC data are available at all times when flow cytometry data is available. | • Section 9.3.3<br>• Table 1<br>• Section 9.5.2<br>• Table 6<br>• Table 7 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Added 30 day window to the duration of the pre-treatment period if required for medical or operational reasons. | To provide the sites with greater operational flexibility. | • Synopsis –<br>  ○ Study Design<br>  ○ Duration of Treatment<br>• Section 9.1<br>• Figure 1<br>• Section 9.1.1<br>• Section 9.1.1.2<br>• Section 9.5.2<br>• Table 6 |
| Clarified the timing of the start of the Randomization Phase | Clarification | • Section 9.1.1<br>• Section 9.1.2<br>• Section 9.5.2<br>• Table 6<br>• Table 7 |
| Increased number of MCI/Prodromal or mild to moderate AD subjects screened for entry into the study | To reflect the higher screen failure rate than originally anticipated | • Synopsis –<br>  ○ Number of Subjects |
| Removal of CD127 cell surface markers | FoxP3 is the most accepted marker to measure T regulatory cells and additional assessment of CD127 is not required. | • Section 9.5.1.5.3<br>• Table 4<br>• Section 9.5.2.1 |
| Made the clinical biochemistry, urinalysis, CBC, lymphocyte subsets, and immunoglobulin tests mandatory at Visit 20, regardless of clinical significance at Visit 19. | For more comprehensive safety data at the second follow-up visit. | • Section 9.5.2<br>• Table 7 |
| Corrected reference to Exclusion Criterion No. 20 (and not to Exclusion #19) in footnote to Table 6 and Table 7 regarding timing of Visit 3 in relation to Visit 2. | Correction | • Section 9.5.2<br>• Table 6<br>• Table 7 |
| Revised details regarding prohibited antiplatelet drugs | To distinguish between those subjects who consent to CSF sample collection and those who do not | • Appendix 2, Listing 2 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015 (per Amendment 01)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised inclusion to allow for enrollment of mild to moderate AD subjects in Stage A and expand the Stage B mild AD cohort to also include moderate AD subjects | To collect safety data in a wider range of AD patients. | • Title Page<br>• Synopsis –<br>  ○ Objectives<br>  ○ Study Design<br>  ○ Number of Subjects<br>  ○ Inclusion/Exclusion Criteria<br>  ○ Study Treatments<br>  ○ Efficacy Assessments<br>  ○ Study Endpoints<br>  ○ Efficacy Analyses<br>  ○ Interim Analyses<br>  ○ Adaptive Randomization<br>  ○ Sample Size<br>• Section 5.3<br>• Section 7<br>• Section 8 (and all subsections)<br>• Section 9.1<br>• Section 9.1.1<br>• Figure 1<br>• Section 9.2.1<br>• Section 9.2.2<br>• Section 9.2.3<br>• Section 9.2.4.3<br>• Section 9.2.4.4<br>• Section 9.3<br>• Section 9.3.1<br>• Section 9.3.2<br>• Section 9.4.1<br>• Section 9.4.3<br>• Section 9.4.4<br>• Section 9.5.1.3.1<br>• Section 9.7.1.1.2<br>• Section 9.7.1.1.3<br>• Section 9.7.1.4<br>• Section 9.7.1.6<br>• Section 9.7.1.6.2<br>• Section 9.7.1.6.3<br>• Section 9.7.1.8.2<br>• Section 9.7.3<br>• Section 9.7.4 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015 (per Amendment 01)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised inclusion criteria for MMSE to ≥16 from ≥20 | The MMSE score is used as a cut-off for the most impaired subject that would be eligible for the study. Lowering the MMSE inclusion from ≥20 to ≥16 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD cohort. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.1 |
| Revised inclusion criteria for FAQ to ≤24 from ≤20 | As for the MMSE, the FAQ score is used as a cut-off for the most impaired subject that would be eligible for the study. Revising the FAQ inclusion from ≤20 to ≤24 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD cohort, and is consistent with an MMSE inclusion of ≥16. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.1 |
| Revised exclusion criteria such that small arachnoid cysts are not necessarily exclusionary | Arachnoid cysts are a common finding in otherwise healthy subjects. Small lesions (<1 cm in diameter) are generally not considered clinically significant and if discovered incidentally no long term follow up is routinely required. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised exclusion criteria for Ig (IgG, IgA, or IgM) to specify that levels below the LLN at Screening or Baseline need not be exclusionary | For subjects with a Screening or Baseline IG level <LLN to be considered for continuation in the study, assessment of clinical significance of the finding will be required. A finding of "not clinically significant" must be agreed between the Investigator and Medical Monitor in order for the subject to continue in the study. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised text to provide instructions for subject assent and associated consent by a legal representative for subjects who the Investigator considers not to have the capacity to consent themselves | With the expansion of the patient population to include moderately demented subjects it was necessary to provide directions regarding the consenting process for subjects considered to be lacking the | • Section 5.3 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015 (per Amendment 01)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | capacity to consent themselves. | |
| Revised number of clinical sites to 30 from 25 | For feasibility purposes. | • Synopsis –<br>  ○ Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Added allowance for Tier 1 and Tier 2 screening assessments to be performed on the same day | Added to provide operational clarity for the sites. | • Section 9.1.1.1<br>• Table 6 |
| Removed requirements for MRIs to include sequences for resting state functional MRI | This was an error and should not have been included in the original protocol. | • Table 6<br>• Table 7 |
| Revised text to clarify that on visits where CSF collection takes place, the CSF collection need not take place on the same day as the cognitive testing for that visit | Added to provide operational clarity for the sites. | • Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised text to clarify that the most important efficacy assessment to keep blinded from safety data is the CDR. | Added to provide operational clarity for the sites. | • Synopsis –<br>  ○ Safety Assessments<br>• Section 9.4.6<br>• Section 9.5.1.5 |
| Revised text to allow PK blood sample and PD blood samples to be taken either shortly before or shortly after the LP on CSF days | Added to provide operational flexibility for the sites. | • Section 9.5.1.4.1<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised Sponsors Grading for Laboratory Values for the following analytes: lymphocytes, neutrophils, albumin, creatinine, phosphate, and potassium serum-high (hyperkalemia) | Corrections made to align with the values for grading used by the central clinical laboratory for this study. | • Appendix 1 |
| Revised details regarding prohibited antiplatelet drugs | Previous version incorrectly referenced a biomarker subgroup. All subjects in this study will need to provide CSF samples. | • Appendix 2; Listing 2 |
| Revised grammar, spelling, etc. | Compliance with current company style guide and for general consistency. | Throughout protocol |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revisions to grammar, spelling, etc. | Compliance with current company style guide and for general consistency | • Throughout protocol |
| Revisions made per new company protocol template | Alignment with current Eisai template | • Synopsis –<br>  ○ Inclusion/Exclusion Criteria<br>• Section 9.1.2.3<br>• Section 9.3.1<br>• Section 9.3.2<br>• Section 9.5 (related subsections)<br>• Section 9.5.4<br>• Section 9.5.4.1<br>• Section 9.5.4.2<br>• Section 9.5.4.3 |
| Clarified classification of MCI due to AD | Clarification that MCI due to AD population will also be consistent with the research criteria for Prodromal AD in that impaired episodic memory is required and will be tested using a list learning task (the International Shopping List Task) | • Synopsis –<br>  ○ Study Design<br>• Section 9.1 |
| Replaced "enroll" with "randomize," pertaining to subject entry into study | Correction to terminology | • Synopsis –<br>  ○ Study Design<br>• Section 9.1<br>• Section 9.3 |
| Added criterion excluding subjects with hepatic impairment and total bilirubin greater than 1.5×ULN or INR greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded. | At request of FDA, exclude subjects who have hepatic impairment | • Synopsis –<br>  ○ Inclusion/Exclusion Criteria<br>• Abbreviation List<br>• Section 9.3.2 |
| Added coagulation parameters for prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR) to screening and baseline procedures | Screen for hepatic impairment | • Synopsis –<br>  ○ Inclusion/Exclusion Criteria<br>• Abbreviation list<br>• Section 9.3.2<br>• Table 4<br>• Table 6<br>• Table 8 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| For subjects who discontinue study drug prematurely, conduct efficacy assessments postdose at same time points as subjects who continue in the study. Added FAQ to this set of efficacy assessments. | To facilitate efficacy analyses, which are based on longitudinal modeling for all subjects | • Synopsis –<br>  ○ Study Design<br>• Section 9.1.2.2<br>• Section 9.3.3<br>• Section 9.5.4.1<br>• Section 9.5.5<br>• Table 7 |
| Delete diagram of E2609 structure | This display is not needed for the protocol. The Investigator's Brochure has this information. | • Section 9.4.2.1 |
| Additional blood samples to be taken at Visits 19 and 20 | Samples are to be put in storage to allow for assessment of immune status at end of study, as needed. | • Synopsis –<br>  ○ Assessments<br>• Table 8 |
| Add subheadings to Section 9.7 describing the primary endpoint analysis, and text clarifying that no multiplicity adjustments will be done to account for the interim analyses | To distinguish clearly the primary analysis and the sensitivity analyses of the primary endpoint | • Synopsis –<br>  ○ Efficacy Analyses<br>• Section 9.7.1.6.1 |
| Clarification of PK sampling upon Early Discontinuation | Additional operational details of the timing of the PK sampling at the ED visit provided | • Section 9.5.1.4.1<br>• Table 7 |
| Clarification of ApoE testing | Clarification that the ApoE genetic testing will be for homozygous or heterozygous E4, versus non-E4 | • Section 9.5.1.4.2 |
| Revision to PK/PD interim analysis text | Confirm that interim PK/PD analysis will be conducted by an independent group | • Section 9.4.6 |
| Addition of text regarding safety signals with E2609 | To provide information on safety-driven dose adjustments | • Synopsis –<br>  ○ Study Design<br>• Section 9.1 |
| Addition of PBMC collection/assessment at Baseline, during treatment, and post-treatment | Recent animal studies have shown an effect of E2609 on this model so they will be added to the 202 clinical study as an additional exploratory assessment. | • Synopsis –<br>  ○ Safety Assessments<br>• Section 9.2.5<br>• Section 9.5.1.5<br>• Table 4<br>• Table 6<br>• Table 7<br>• Table 8 |
| Stipulate that exploratory biomarker analyses may be conducted using blood or CSF samples that may have been drawn for other purposes | To allow more flexibility for possible exploratory biomarker studies associated with study drug or disease, including miRNA and DNA | • Synopsis –<br>  ○ Assessments<br>• Abbreviation list<br>• Section 9.5.1.4.2<br>• Section 9.5.1.5.12<br>• Table 6 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | | • Table 7 |
| Prohibit concomitant medications that are strong CYP3A4, inhibitors, but clarify that no restrictions are needed for other CYP3A4 inhibitors, CYP3A4 inducers, or CES2 inhibitors | At request of FDA, in light of finding that inhibition of CYP3A4 by a reference agent increases plasma levels of E2609 | • Synopsis –<br>○ Concomitant Drug/Therapy<br>• Section 7.1<br>• Section 9.4.7<br>• Appendix 2, Listing 6 |
| Addition of tests for viral characterization at Baseline | To confirm by serology information of subjects prior exposure to common viruses pre-dosing with study drug | • Section 9.5.1.2.2<br>• Table 4<br>• Table 6<br>• Table 8 |
| Use of a centralized dermatologist assessment via photography | A centralized approach, using standardized photography, to FDA-required serial dermatological assessments will be employed for consistency of assessments between sites and for consistency of longitudinal assessments of individual subjects. | • Synopsis –<br>○ Safety Assessments<br>• Section 9.2.5<br>• Section 9.5.1.5<br>• Section 9.5.1.5.8<br>• Table 6<br>• Table 7 |
| Removal of testing for benzodiazepines or opioids as part exclusion criteria #35 | To differentiate appropriate medicinal use from recreational drug use or abuse | • Synopsis –<br>○ Exclusion Criteria<br>• Section 9.3.2 |
| Addition of analysis of other covariates such as adjusted hippocampal volume will be studied | Hippocampal volume has been shown to correlate with rate of cognitive decline and as such is a key covariate to be used in the analyses. | • Synopsis –<br>○ Analysis of Primary Endpoint<br>• Section 9.7.1.6.1 |
| Addition of clarifications to ophthalmic examination | To provide more detail around the requirements for the ophthalmic exam | • Synopsis –<br>○ Safety Assessments<br>• Section 9.5.1.5.13<br>• Table 6<br>• Table 7 |
| Addition of details regarding specific method of CSF collection (ie, gravity drip) | Use of materials required for suction method when collecting CSF can affect the PD data and so it is important to make it clear that only the gravity drip method can be used for collecting CSF in this study for protecting the quality and the consistency of the CSF PD data. | • Section 9.5.1.3.3<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Addition of specific testing for B12 levels at Screening | Abnormally low serum vitamin B12 levels are exclusionary for the study (exclusion criterion 8) but a | • Synopsis –<br>○ Exclusion Criteria<br>• Section 9.3.2 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | blood draw for Vitamin B12 was inadvertently missed out of Table 6 in protocol version 1. | • Section 9.5.1.2.3<br>• Figure 2<br>• Table 6 |
| Addition of details regard AEs that might be signals of possible drug abuse potential | Changed terminology re: collection of additional information for AEs that might be signals of possible abuse potential. No longer use the word "narrative" in order to avoid potential confusion with standard clinical trial narratives eg, for serious adverse events, adverse events leading to withdrawal, etc. | • Synopsis –<br>○ Safety Assessments<br>• Section 9.2.5<br>• Section 9.5.1.5.1<br>• Appendix 4 |
| Addition of clarification regarding position for taking vital signs (ie, supine) | The American Heart Association guidelines only mention supine, standing, and sitting as positions for taking HR and BP measurements. Therefore, have changed required position from semi-supine to sitting. | • Section 9.5.1.5.4<br>• Table 6<br>• Table 7 |
| Stipulated that study drugs are to be taken with food | For consistency of treatment conditions | • Section 9.5.1.4.1 |
| Change to list of Study Specific AEs which should be considered SAEs | Eisai's standard procedures have changed such that non-serious study specific adverse events of interest are no longer reported to Eisai Product Safety; instead, any additional information required for such non-serious adverse events will be obtained through other methods. In addition, certain events (new onset seizures, ocular herpes) are now to be classified as serious as important medical events, regardless of whether they meet standard ICH serious criteria. | • Section 9.5.1.5.1<br>• Section 9.5.1.5.2 |
| Increased blood volume for PK | To match collection tubes and ensure sufficient sample for planned assays | • Table 8 |
| Corrected error in definition of PK analysis set | For accuracy | • Synopsis –<br>○ Study Endpoints<br>• Section 9.7.1.2 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Addition of details regarding discontinuation of study drug | To clearly and consistently differentiate "discontinuation from study drug" from "withdrawal from study" | • Synopsis<br>• Section 7<br>• Section 9.1.2.1<br>• Section 9.2.5<br>• Section 9.3.3<br>• Table 1<br>• Table 2<br>• Section 9.4.1<br>• Section 9.4.4<br>• Section 9.5.1.5.1<br>• Section 9.5.1.5.3<br>• Section 9.5.5 |
| Re-ordered prohibited medication lists | For consistency, all lists re-ordered in alphabetical order of generic drug name, and footnotes revised for overall consistency | • Appendix 2 |
| Moved nefazodone from Listing 9 to Listing 6 | Nefazodone is a strong CYP3A4 inhibitor and is therefore prohibited. | • Appendix 2 |

# 1 TITLE PAGE


## Clinical Study Protocol

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01 and 05) |
| **Sponsor:** | Eisai Inc.<br>100 Tice Boulevard<br>Woodcliff Lake,<br>New Jersey 07677<br>United States<br><br>Eisai Ltd.<br>European Knowledge Centre<br>Mosquito Way<br>Hatfield, Hertfordshire<br>AL10 9SN<br>United Kingdom<br><br>Eisai Co., Ltd.<br>4-6-10 Koishikawa<br>Bunkyo-Ku,<br>Tokyo 112 8088<br>Japan |
| **Investigational Product Name:** | E2609 |
| **Indication:** | Alzheimer's disease |
| **Phase:** | 2 |
| **Approval Date:** | V1.0 15 Jul 2014 (original protocol)<br>V2.0 21 Oct 2014 (revised original protocol)<br>V3.0 28 May 2015 (Amendment 01)<br>V4.0 05 Nov 2015 (Amendment 02)<br>V5.0 06 Feb 2016 (Amendment 03)<br>V6.0 29 Jun 2016 (Amendment 04)<br>V7.0 26 Sep 2016 (Amendment 05) |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |
| **GCP Statement:** | This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities. |
| **Confidentiality Statement:** | This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study. |

# 2 CLINICAL PROTOCOL SYNOPSIS

**Compound No.:**

E2609

**Name of Active Ingredient:**

*N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

**Study Protocol Title**

A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01 and 05)

**Investigators**

Investigators in the United States only (revised per Amendment 05)

**Sites**

Approximately 35 sites, United States only (revised per Amendments 01, 02, 04, and 05)

**Study Period and Phase of Development**

Approximately 32 months (revised per Amendment 05)

Phase 2

**Objectives**

**Primary Objective** (revised per Amendment 05)

- To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with Mild to Moderate Dementia due to Alzheimer's Disease (referred to as mild to moderate AD throughout the protocol) (revised per Amendment 01)

**Secondary Objectives** (revised per Amendments 02 and 05)

- To characterize the plasma and cerebrospinal fluid (CSF) pharmacokinetics (PK) of E2609
- To assess the effects of E2609 on Aβ(1-x) and Aβ(1-42) in CSF from 4 weeks and up to 18 months of treatment

**Exploratory Objectives**

(revised per Amendments 01, 02, 04, and 05)

- To explore the effects of E2609 on CSF Aβ(1-40) and beta (β)-amyloid converting enzyme 1 (BACE1) measurements from 4 weeks and up to 18 months of treatment
- To explore the effects of E2609 compared with placebo on various biomarkers. Biomarkers to be explored may include but are not limited to:
    a. CSF biomarkers of neurodegeneration (eg, total tau [t-tau], phosphorylated-tau [p-tau]) after 18 months of treatment
    b. Plasma and CSF amyloid, and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment and during post-treatment follow-up

c. Total hippocampal atrophy at 12 and 18 months of treatment, as measured by volumetric magnetic resonance imaging (vMRI)
d. vMRI measurements including left and right hippocampal volume, whole brain volume and total ventricular volume at 6, 12, and 18 months of treatment
e. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)

- To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during posttreatment follow-up, by assessment of:
  a. The Alzheimer's Disease Assessment Scale – cognitive subscale ($ADAS\text{-}cog_{14}$)
  b. The Clinical Dementia Rating (CDR) scale
  c. The Mini-Mental State Examination (MMSE)
  d. The International Shopping List Task (ISLT)
  e. The CogState Brief Battery (CBB)
  f. The Functional Assessment Questionnaire (FAQ; also known as the Functional Activities Questionnaire)
- To explore the relationship between the treatment effects of E2609 on measured clinical efficacy scales (eg, MMSE, CDR) and its effects on CSF amyloid, CSF amyloid isoforms, brain amyloid, and vMRI
- To explore relationships between both E2609 dose and exposure, with pharmacodynamic (PD) and safety endpoints

**Study Design**

This will be a multicenter, placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild to moderate AD. A common set of inclusion criteria, consistent with the National Institute on Aging–Alzheimer's Association (NIA-AA) clinical research criteria for Mild Cognitive Impairment (MCI) due to Alzheimer's Disease (AD) or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with the criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study consists of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days, plus an additional window of up to 30 days if required [revised per Amendment 02]) includes a Screening Visit (Visit 1) and a Baseline Visit (Visit 2). All screening assessments (within 4 distinct tiers) must be completed, and eligibility to continue in the study confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

The study will be limited to approximately 35 sites in the United States. (revised per Amendments 01, 02, and 04) Subjects will be randomized 1:1:1:1 to 4 treatment groups (5, 15, or 50 mg E2609 or placebo) within each of the 2 clinical populations. (revised per Amendments 01, 04, and 05) In

addition to the placebo group, 3 E2609 doses will be used to reduce CSF amyloid β levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/pharmacodynamic (PD) modeling has shown that these doses should achieve these targets when administered once daily (QD) with food, and these doses will be evaluated based on the 4-week (or later) assessment of CSF Aβ(1-x) from subjects who provide voluntary consent for CSF measurement. (revised per Amendment 02)

Safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the 1st subject is randomized into the study, an independent data safety monitoring board (DSMB; including at least 1 immunologist) will review all safety data in an unblinded manner. The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. (revised per Amendments 01, 04, and 05)

Interim analyses of the E2609 plasma PK for all subjects and the E2609 CSF PK and PD profiles will be performed on baseline data and samples collected after at least 4 weeks of treatment. (revised per Amendment 05) These interim analyses, as well as analyses of safety data, will be performed on an ongoing basis throughout the study. Refer to the Interim Analysis section for more detail. These data will be used to evaluate the CSF PD effects of E2609 doses, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels. (revised per Amendments 01 and 02) The median and mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks or more of treatment for each dose of E2609 and the 90% confidence interval (CI) for the median will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data and will relate the average steady state plasma concentration of E2609 to CSF Aβ(1-x) percentage reduction from baseline determined after at least 4 weeks of dosing. (revised per Amendments 01, 02, 03, 04 and 05)

Once subjects have completed at least 12 weeks of treatment (or discontinued study drug early) an interim safety analysis will be conducted by Eisai and the DSMB. Subjects will continue study drug while the DSMB reviews all the available safety data. (revised per Amendments 01, 04, and 05)

If there are safety signals with one of the E2609 dose groups that would require dose adjustment, changes to dose will be reflected in an amendment to the protocol. Information on how these subjects will be handled in the primary analysis will be described in the Statistical Analysis Plan.

**Early Discontinuation**

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug. (revised per Amendments 04 and 05)

**Follow-Up**

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 4 post-treatment Follow-Up Visits: 2, 4, 8, and 12 weeks after the last dose of study drug. If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the post-treatment Follow-Up Period. (revised per Amendment 04)

**Number of Subjects**

Approximately 400 MCI/Prodromal or mild to moderate AD subjects will be screened to provide approximately 60 (±20%) randomized subjects (a target of approximately 15 subjects per treatment arm). There will be no limit to the number of subjects randomized from either clinical cohort. (revised per Amendments 01, 02, 04, and 05)

**Inclusion Criteria**

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD or AD dementia and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at Screening Visit 1:**
(revised per Amendment 02)

   a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation
   b. Cognitive impairment of at least 1 standard deviation (SD) from age adjusted norms in delayed recall on the ISLT. Alternatively, cognitive impairment of at least 0.5 SD from age-adjusted norms in delayed recall on the ISLT plus impairment of at least 1 SD from age-adjusted norms in at least 1 other computerized learning and memory test (ISLT immediate recall, or 1 of the learning and memory components of the CBB). (revised per Amendment 02)
   c. FAQ ≤24 (revised per Amendment 01)
   d. MMSE ≥16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading; an historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group (revised per Amendment 02)
3. Male or female, age 50 to 85 years, inclusive at time of consent
4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.
5. If receiving acetylcholinesterase inhibitors (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry

into the study.

6. Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization.

**Exclusion Criteria (revised per Amendment 04)**

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or magnetic resonance imaging (MRI)
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and <1 cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could, in the opinion of the investigator, confound the MCI/Prodromal or mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendments 01 and 02)
7. A score of ≥8 on the 15-item Geriatric Depression Scale at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the lower limit of normal (LLN) for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
12. Any contraindications to lumbar puncture (LP) for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity). Only applicable to subjects consenting to CSF sample collection (revised per

Amendment 02)

13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization
20. Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below population-adjusted LLN at Screening or Baseline and confirmed by a repeat test conducted 1 week after the initial test. The population-adjusted LLN for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are 396, 157, and 74 cells/μL respectively. (revised per Amendment 02)
23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the Investigator and the Medical Monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of clinical immunodeficiency. The discussion with the Medical Monitor should include a detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)
24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate electrocardiograms (ECGs). A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.

26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute at Screening or Baseline
29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.
33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo). Diagnosis of an underlying disease causing hypopigmentation is not necessary for exclusion if the clinical presentation is consistent with such a condition. Hypopigmentation associated with scarring need not be exclusionary. (revised per Amendment 02)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding

informed consent

41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the 1st dose of study drug.
43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period and for 28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.
    - Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
      (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

**Study Treatments**

E2609 tablets of 5-, 10-, and 25-mg dose strengths will be supplied. Placebo tablets to match E2609 will be of identical appearance. Each subject will receive 2 tablets, which when combined will make up the required doses of E2609 or placebo, to be administered orally QD with food. (revised per Amendment 05)

**Duration of Treatment**

The maximum duration of a subject's participation in the study will be approximately 2 years, comprising:

- Screening and Baseline Periods (Prerandomization Phase): up to 60 days, plus an additional window of up to 30 days if required (revised per Amendment 02)

  (In subjects who have an active infection within 4 weeks of the planned randomization date, the duration of the pre-randomization phase can be extended by up to 4 weeks to allow additional time for resolution of the infection.)
- Treatment Period (Randomization Phase): up to 78 weeks
- Follow-Up Period (Randomization Phase): 12 weeks (post last dose)

**Concomitant Drug/Therapy**

(revised per Amendment 04)

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit (see Appendix 2 for a detailed listing of these agents):

- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization. However, during the treatment period of the study, short term (not more than 14 days) use of steroids up to the equivalent of prednisolone 40 mg QD is permitted after discussion with the Medical Monitor. Dosing with study drug should be suspended from the time steroid treatment is started. Complete blood count and lymphocyte subsets should be determined prior to starting steroid treatment and continue to be monitored weekly. Study drug may be resumed after discussion with the Medical Monitor when the following conditions are met: (1) treatment with steroids has been completed for at least 1 week; (2) total lymphocytes not <LLN; (3) no lymphocyte subsets are below the discontinuation threshold; (4) the investigator considers that the medical condition which required treatment with steroids has improved or resolved. Weekly testing of lymphocyte subset counts and CBC with differentials is required for 4 weeks following resumption of study drug administration. (revised per Amendment 04)

Subjects taking AChEIs or memantine must meet the following criteria in order to be included in the primary analyses:

- On a stable dose for 12 weeks before the baseline cognitive assessments at Visit 2
- Remain on a stable dose while on study

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for any efficacy analyses. (revised per Amendment 05)

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed. Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before randomization. They may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 04)
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if, in the opinion of the investigator, this will not interfere with study procedures or subject safety, and are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks

Antiplatelet therapy: (revised per Amendment 04)

- For subjects who consent to CSF sample collection: Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) are permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.
- For subjects who do not consent to CSF sample collection: Aspirin and clopidogrel, individually or in combination, are permitted.

**Assessments**

**Efficacy Assessments**

Alzheimer's Disease Assessment Scale - cognitive subscale: The 14-item version will be used since it is considered more relevant for subjects with MCI/Prodromal AD or mild AD.

Clinical Dementia Rating: Assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

Mini-Mental State Examination: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing.

International Shopping List Task: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall.

CogState Brief Battery: A computer-based battery comprising 4 cognitive tests:

- Detection – a simple reaction time test. Speed of response is the measure.
- Identification – a simple choice reaction time test. Speed of response is the measure.
- One Card Back – a simple working memory test. Accuracy of response is the measure.
- One Card Learning – a visual learning and memory test. Accuracy of response is the measure.

Functional Assessment Questionnaire: The FAQ has 10 items concerned with performing daily tasks necessary for independent living. The caregiver or informant provides performance ratings on 10 complex activities of daily living performed within the preceding 4 weeks. (revised per Amendment 04)

Volumetric Magnetic Resonance Imaging: vMRI will be used to evaluate disease modification, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs.

**Pharmacokinetic Assessments**

Blood samples will be collected for the determination of the concentrations of E2609. For subjects who consent to CSF sample collection, CSF samples will be collected for the determination of E2609 concentrations. (revised per Amendment 02) Analyses of metabolite concentrations may be performed depending on emerging data from other studies with E2609.

**Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments**

Brain atrophy will be measured by vMRI: see Efficacy Assessments (above).

The soluble biomarkers Aβ(1-x), Aβ(1-42), (Aβ(1-40), total tau (t-tau), and p-tau will be measured in subjects who consent to CSF sample collection (revised per Amendment 02). BACE1 levels and activity in CSF will also be measured in subjects who consent to CSF sample collection (revised per Amendment 02). Other exploratory biomarkers and amyloid isoforms (eg, Aβ[1-40]) may also be evaluated in plasma or CSF. (revised per Amendment 04) Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

Amyloid PET imaging will be used to confirm that all subjects eligible for progression to the Baseline Period have amyloid deposition in the brain. An historical amyloid positive PET scan may be used, if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02) Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses. (revised per Amendments 02 and 05)

Apolipoprotein E (*ApoE*) and N-acetyltransferase 2 (*NAT2)* genotyping/phenotyping will be conducted. *ApoE4* homozygous or heterozygous status versus non-carriers and *NAT2* status will be used in the statistical analysis to determine the effects on treatment response and safety. Remaining genomic DNA may also be stored for up to 15 years to be used to examine the role of DNA sequence variability on the absorption, distribution, metabolism, and elimination of E2609, development of adverse events (AEs), as well as the underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single-nucleotide polymorphisms with PK, safety, or PD data.

**Safety Assessments**

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR. (revised per Amendment 01) Routine safety assessments will include the monitoring and recording all AEs and serious adverse events (SAEs), monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

Complete blood counts and lymphocyte subset absolute counts and percentages will be measured (by a centralized laboratory) every week for the 1st month, every 2 weeks for the next 2 months (Months 2 and 3) and monthly for the next 3 months (Months 4, 5, and 6). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at all 4 Follow-Up Visits at 2, 4, 8, and 12 weeks after the last dose of study drug. Serum IgG, IgA, and IgM will be monitored monthly for the 1st 3 months, at 6, 12, and 18 months, and at the Follow-Up Visits that occur 4, 8, and 12 weeks after the last dose of study drug. (revised per Amendment 04)

Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and

post-treatment for exploratory immunomodulatory and immune-based analyses.

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at baseline and at 3-month intervals during the Treatment Period. These assessments will specifically include evaluation of any areas of depigmentation or rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregivers/ informants will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so such AEs can be reviewed promptly.

Baseline and on-study blood and DNA samples will be taken and stored for all subjects, and CSF samples will be taken and stored for all subjects from whom CSF samples were collected (revised per Amendments 02 and 04). These samples may be tested for exploratory biomarkers associated with study drug or disease, or in the event that a subject develops AEs that warrant further investigation (eg, to test if a subject with a treatment-emergent infection was exposed to any suspected infective agents before treatment with study drug).

Safety brain MRI assessments will be performed at Screening, at 6, 12, and 18 months during the Treatment Period and at the final Follow-Up Visit. Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Full neurologic examinations will be performed at Baseline, at 6, 12, and 18 months, and at the 4- and 12-week Follow-Up Visits, by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. The neurologic examinations will include muscle strength testing and assessment of cranial nerves including olfaction, with the use of the Brief Small Identification Test, as well as other parts of the CNS. (revised per Amendment 04)

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments will include the ADAS-$cog_{14}$, MMSE, and CBB.

An assessment of suicidality using the C-SSRS will be performed at Screening and Baseline and at regular intervals throughout the Treatment and Follow-Up Periods.

An ophthalmic examination (including retinal examination) will be conducted at Baseline. An additional examination will be conducted if the subject experiences visual disturbances during the course of the study.

A number of safety-related criteria for discontinuation of study drug are specified for the study.

**Bioanalytical Methods**

Plasma and CSF concentrations of E2609 will be measured by a validated liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) in both CSF and plasma will be measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendment 04)

BACE1 levels and activity may be measured using a customized assay. Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

**Statistical Methods**

All statistical tests will be based on the 5% (2-sided) level of significance. (revised per Amendment 05)

**Study Endpoints**

**Primary Endpoint**

- Safety and tolerability, which include incidence of treatment-emergent adverse events (TEAEs) and SAEs, laboratory parameters, vital signs, and ECG parameters (revised per Amendment 05)

**Secondary Endpoints**

(revised per Amendments 02 and 05)

- % reduction of Aβ(1-x) and Aβ(1-42) in CSF relative to baseline after at least 4 weeks and 18 months of treatment
- The population PK parameters of E2609 in CSF and plasma, including the effect of intrinsic and extrinsic factors (including NAT2 phenotype)

**Exploratory Endpoints**

(revised per Amendments 01, 02, 04, and 05)

Change from baseline in:

- CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months of treatment
- CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- CSF amyloid and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- Total hippocampal volume at 12 and 18 months of treatment as measured by vMRI
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months as measured by vMRI
- Amyloid PET standardized uptake value ratio (SUVR) composite at 18 months for brain amyloid levels
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog$_{14}$, CDR, MMSE, ISLT, CBB, and FAQ

**Analysis Sets**

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose exploratory efficacy measurement. (revised per Amendment 05)
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 post-treatment PD measurement.

**Efficacy and Biomarker Analyses** (revised per Amendment 05)

**Analysis for the Primary Endpoint**

There is no primary efficacy endpoint. (revised per Amendment 05)

**Analysis for the Secondary Endpoints**

An mixed-effects model with repeated measures (MMRM) will be used to analyze the following secondary endpoint:

- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) from 4 weeks and up to 18 months. Data from early discontinuations will also be included. (revised per Amendment 05)

**Analysis for Exploratory Endpoints**

(revised per Amendments 01, 02, 04, and 05)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months of treatment
- Change from baseline in CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Change from baseline in plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during post-treatment follow-up
- Change from baseline in CSF amyloid and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- Change from baseline in total hippocampal atrophy at 12 and 18 months as measured by vMRI
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months as measured by vMRI
- Change from baseline in Amyloid PET SUVR composite at 18 months for brain amyloid levels

The following efficacy endpoints will be summarized using descriptive statistics:

- Change from baseline in the clinical assessments: ADAS-cog$_{14}$, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months

The relationship between efficacy endpoints and biomarker endpoints will be explored using

correlation analysis.

**Pharmacokinetic Analyses**

The PK Analysis Set will be used for E2609 concentration listings and for summaries of E2609 concentrations in plasma and CSF by dose and day. E2609 metabolite PK data may also be listed and summarized. (revised per Amendment 05)

A population PK approach will be used to characterize the plasma PK of E2609. For this approach, plasma PK data from this study will be pooled with relevant data from Phase 1 studies. As appropriate, the effect of covariates on the PK of E2609 will be evaluated. The PK model will be parameterized for oral clearance (CL/F) and apparent volume of distribution (Vz/F) for E2609. Derived exposure parameters such as steady state area under the concentration time curve (AUC) and average concentration ($C_{avg}$) of E2609 and other derived parameters will be calculated from the model using the individual estimates parameterized for oral clearance and dosing history. (revised per Amendment 04)

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). The percentage change from baseline in CSF Aβ(1-x), Aβ(1-40), Aβ(1-42), t-tau, p-tau, and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months will be analyzed and presented graphically. (revised per Amendments 04 and 05) Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status. Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels, amyloid load on PET, vMRI and E2609 dose, plasma and CSF exposure will be initially explored graphically and any emergent relationship will be explored through population PK/PD modeling. Additionally, the relationship between CSF exposure to E2609 and the change from baseline for 18 months in the ADAS-cog, the CDR, and the MMSE will be explored graphically. (revised per Amendments 04 and 05)

Additionally, the relationship between plasma exposures of E2609 and select lymphocyte parameters will be explored graphically, and any emergent relationship will be explored using population-based modeling methods. (revised per Amendment 04)

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. Further information is in the "Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments" section. Details of pharmacogenomic testing may be provided and reported separately.

**Safety Analyses**

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements, and cognitive decline assessment such as CBB will be summarized by treatment group using descriptive statistics. (revised

per Amendment 05)

Lymphocyte Subsets

Lymphocyte subsets, including but not limited to, CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages]) and regulatory T cells will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose.

Serum IgG, IgM, IgA will be measured and summarized in the same manner as other laboratory parameters. (revised per Amendment 04)

**Interim Analyses**

In order to make decisions about the remainder of the study as well as the full E2609 clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. Investigators, other clinical site staff, subjects, caregivers/informants and study team will remain blinded to study treatment. (revised per Amendments 03 and 05)

An interim safety analysis will also be conducted when 60 subjects (±20%) have completed 12 weeks of treatment (or discontinue study drug early). (revised per Amendments 01, 03, 04, and 05)

**Stratification**

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

**Sample Size Rationale**

A total of 15 subjects per dose is deemed sufficient to derive adequate safety and PK/PD data to aid in the selection of appropriate doses and the design of the Phase 3 studies that may be planned subsequently. (revised per Amendment 04)

# 3 TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES



## LIST OF IN-TEXT FIGURES



## LIST OF APPENDICES

# 4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| Aβ | amyloid β |
| Aβ(1-x) | amyloid β (1-x) (ie, the amyloid β monomer from amino acid 1 to x [eg, 1-42]) |
| AChEI | Acetylcholinesterase inhibitor |
| AD | Alzheimer's disease |
| ADAS-cog | Alzheimer's Disease Assessment Scale - cognitive subscale |
| AE | Adverse Event |
| ApoE | Apolipoprotein E |
| AUC | area under the concentration x time curve |
| $AUC_{(0\text{-}24h)ss}$ | area under the concentration x time curve at steady state from time zero to 24 hours |
| BACE1 | Beta (β)-amyloid converting enzyme 1 |
| BP | blood pressure |
| bpm | beats per minute |
| CBB | CogState Brief Battery |
| CBC | complete blood count |
| CBP | childbearing potential |
| CDR | Clinical Dementia Rating |
| CES2 | carboxyesterase-2 |
| CFR | Code of Federal Regulations |
| $C_{max,ss}$ | maximum plasma concentration at steady state |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| CI | confidence interval |
| CRA | clinical research associate |
| CRF | case report form |
| CRO | contract research organization |
| CSF | cerebrospinal fluid |
| $C_{ss,av}$ | average steady-state concentration |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CTA | Clinical Trial Agreement |
| CYP | cytochrome P450 |
| DSMB | data safety monitoring board |
| ECG | electrocardiogram |
| eCRF | electronic case report form |

| Abbreviation | Term |
|---|---|
| ED | early discontinuation |
| ELISA | enzyme-linked immunosorbent assay |
| FAQ | Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire) |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FLAIR | fluid-attenuated inversion recovery |
| GCP | Good Clinical Practice |
| GDS | Geriatric Depression Scale |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |
| HCVAb | hepatitis C virus antibody |
| HSV | herpes simplex virus |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ID | identifier |
| IEC | Independent Ethics Committee |
| Ig | immunoglobulin (eg, IgA, IgG, IgM) |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISLT | International Shopping List Task |
| IxRS | interactive voice and web response system |
| LLN | lower limit of normal |
| LNH | low/normal/high |
| LP | lumbar puncture |
| MAD | multiple ascending dose |
| MCI | mild cognitive impairment |
| MCI/Prodromal | Mild Cognitive Impairment due to Alzheimer's Disease/ Prodromal Alzheimer's Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mild to moderate AD | mild to moderate dementia due to Alzheimer's Disease |
| miRNA | micro-ribonucleic acid |
| MMRM | mixed-effects model with repeated measures |
| MMSE | Mini-Mental State Examination |
| MRI | magnetic resonance imaging |

| Abbreviation | Term |
|---|---|
| NAT2 | N-acetyltransferase 2 |
| NIA-AA | National Institute on Aging-Alzheimer's Association |
| PBMC | peripheral blood mononuclear cell |
| PD | Pharmacodynamic(s) |
| PET | positron emission tomography |
| PGx | pharmacogenomic(s) |
| PK | pharmacokinetic(s) |
| PRN | Pro re nata |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| p-tau | phosphorylated-tau |
| QD | once daily |
| QTc | corrected QT interval |
| QTcF | QTc interval calculated using Fridericia's formula |
| R | randomization |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reaction |
| SUVR | standardized uptake value ratio |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |
| TEMAV | treatment-emergent markedly abnormal laboratory values |
| t-tau | total tau |
| ULN | upper limit of normal |
| UNS | unscheduled |
| vMRI | volumetric magnetic resonance imaging |
| WHO DD | World Health Organization Drug Dictionary |
| β-hCG | beta-human chorionic gonadotropin |

# 5 ETHICS

## 5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA][s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigators or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

## 5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (CFR) (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

- European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved European Union member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

## 5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject and the identified caregiver or informant, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or understand it or if the identified caregiver or informant is unable to read, an impartial witness should be present during the entire informed consent discussion. If, in the Investigator's opinion, a subject lacks capacity to consent, the subject's assent should be obtained in addition to the written informed consent of a legal representative (capacity to consent and definition of legal representative should be determined in accordance with applicable local laws and regulations). (revised per Amendment 01) After the ICF and any other written information to be provided to subjects is read and explained to the subject and the identified caregiver or informant, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified caregiver or informant should also consent to supporting the subject's participation in the study and will be provided with a separate written ICF for his or her participation in the study, to be signed before he or she participates in any further aspects of the study.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified caregiver or informant must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified caregiver or informant will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified caregiver or informant should be

informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

All subjects will also be asked to provide written consent for cerebrospinal fluid (CSF) sampling at Baseline and after receiving study drug for from 4 weeks and up to 18 months (or at Early Discontinuation). This consent for CSF sample collection is not required for study eligibility. (revised per Amendments 02 and 05)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects and will be via a separate, optional CSF consent form for the study. (revised per Amendment 04)

# 6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 35 investigational sites in the United States. (revised per Amendments 01, 02, 04, and 05)

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

# 7 INTRODUCTION

At this time, there is no cure for Alzheimer's disease (AD), no known way of slowing down the progression of this disease, and no approved treatment available to reverse the deterioration. There is, therefore, an urgent unmet medical need for drugs that slow or prevent disease progression. Beta-amyloid converting enzyme 1 (BACE1) is a key enzyme responsible for the production of amyloid β (Aβ) peptides and plaque formation, and several reports have described elevated levels of BACE1 in AD brains (Coulson, et al., 2010; Lu, et al., 2012). Once amyloid plaques form, Aβ causes BACE1 levels to increase further, thus accelerating Aβ generation and plaque growth via a positive feedback loop. Therefore, BACE1 is a promising target for modifying or treating AD.

It is now widely accepted that mild cognitive impairment (MCI) due to AD and mild to moderate AD dementia are stages on a single disease spectrum, which follows an Alzheimer's pathological cascade. (revised per Amendment 01) Recent consensus papers from the international workgroups of the National Institute on Aging-Alzheimer's Association (NIA-AA), have endorsed this hypothesis (Albert, et al., 2011; Jack, et al., 2011; McKhann, et al., 2011; Rosen, et al., 1984; Sperling, et al., 2011).

From a clinical standpoint, demonstration of an effect on slowing disease course is hampered by the lack of sensitive tools for detecting relatively small changes in progression or treatment effect especially in early disease. In addition, drugs that are expected to slow disease progression require longer study durations to ensure adequate separation from placebo. These challenges have resulted in the use of biomarkers as surrogates for clinical effect in Phase 2 studies, in order to facilitate the development process for disease modifying agents. However, subsequent Phase 3 AD studies based solely on biomarker findings in Phase 2 have failed to show clinical effect, due, in part, to the fact that biomarkers may not predict clinical outcomes for potential disease modifying agents. These findings underscore the need for innovative approaches to clinical study design for measuring the effect of treatment.

E2609 is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, E2609 inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in cerebrospinal fluid (CSF) and plasma (rat, guinea pig, and monkey). In humans, E2609 has been shown to inhibit BACE1 enzyme activity in CSF and lower the levels of Aβ, including amyloid beta monomer from amino acid 1 to x (Aβ[1-x]), Aβ(1-40) and Aβ(1-42), in CSF both in vitro and in vivo. See the Investigator's Brochure for additional information. The target indication for E2609 is therefore treatment and disease modification of AD.

The present clinical study is a Phase 2 study for the E2609 program, and is designed to establish safety in subjects with Mild Cognitive Impairment due to Alzheimer's Disease/Prodromal Alzheimer's Disease (referred to as MCI/Prodromal throughout the protocol) and in subjects with mild to moderate AD. (revised per Amendment 05) Results from this study will guide both the decision to move into Phase 3 development and the selection of the dose strengths to be taken into Phase 3.

In the MCI/Prodromal and mild to moderate AD population, this study will compare placebo and 3 oral doses of E2609 (5, 15, and 50 mg) administered once daily (QD) for 18 months. (revised per Amendment 05)

This study will include interim evaluations of the pharmacokinetic (PK), pharmacodynamic (PD), safety, and tolerability of chronic dosing with E2609. (revised per Amendment 05) Furthermore, there will be close monitoring of safety by an independent data safety monitoring board (DSMB), including a formal safety review as soon as the randomized subjects (n=60, ±20%) have completed at least 12 weeks of treatment, have discontinued study drug or have withdrawn from the study. (revised per Amendments 04 and 05) The study also includes a number of exclusion criteria, specific blinded safety monitoring procedures and safety criteria for discontinuation of study drug in light of the preclinical and clinical safety data collected to date following administration of E2609.

## 7.1 Nonclinical and Clinical Safety Data

The toxicity of E2609 has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomologus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by E2609 in a clinical setting. Further details of the nonclinical data to date with E2609 can be found in the Investigator's Brochure.

The clinical program to date includes 6 Phase 1 studies:

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, single ascending dose (SAD) study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50-mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled MAD study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of E2609 and the PD effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of E2609. It also investigated the effects of E2609 on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [$^{14}$C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of E2609 under fasted

conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) was a randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with E2609. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with E2609. In elderly subjects treated with 50 mg of E2609, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTc interval calculated using Fridericia's formula (QTcF) from baseline (14.9 msec at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of E2609 might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that E2609 altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of E2609. A single dose of E2609 up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, E2609 administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of E2609 on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP3A4] and carboxyesterase-2 [CES2]) increased by

approximately 70% the area under the concentration × time curve (AUC) of E2609. Consequently, strong inhibitors of CY3A4 will be prohibited in this study.

Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of E2609. Therefore, no restrictions are required for the use of concomitant medications which are known to be inducers of CYP450 enzymes. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of E2609 when coadministered with E2609 but not when dosed at least 2 hours apart from E2609. E2609 (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of E2609. Therefore, on the basis of drug interaction considerations, the only restriction of concomitant medications is that for strong inhibitors of CYP3A4.

# 8 STUDY OBJECTIVES

## 8.1 Primary Objective

(revised per Amendment 05)

The primary objective is:

- To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with mild to moderate AD (revised per Amendment 01)

## 8.2 Secondary Objectives

The secondary objectives are: (revised per Amendments 02 and 05)

- To characterize the plasma and CSF PK of E2609
- To assess the effects of E2609 on Aβ(1-x) and Aβ(1-42) in CSF from 4 weeks and at 18 months of treatment

## 8.3 Exploratory Objectives

(revised per Amendments 01,02, 04, and 05)

The exploratory objectives are:

- To explore the effects of E2609 compared on CSF Aβ(1-40) and BACE1 measurements from 4 weeks and up to 18 months of treatment
- To explore the effects of E2609 compared with placebo on various biomarkers. Biomarkers to be explored may include, but not limited to:
  a. CSF biomarkers of neurodegeneration (eg, total tau [t-tau], phosphorylated-tau [p-tau]) after 18 months of treatment
  b. Plasma and CSF amyloid, and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment and during post-treatment follow-up
  c. Total hippocampal atrophy at 12 and 18 months of treatment, as measured by volumetric magnetic resonance imaging (vMRI)
  d. vMRI measurements including left and right hippocampal volume, whole brain volume, and total ventricular volume at 6, 12, and 18 months of treatment
  e. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)

- To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during posttreatment follow-up by assessment of:
  a. The Alzheimer's Disease Assessment Scale – cognitive subscale ($ADAS\text{-}cog_{14}$)

b. The Clinical Dementia Rating (CDR) scale
c. The Mini-Mental State Examination (MMSE)
d. The International Shopping List Task (ISLT)
e. The CogState Brief Battery (CBB)

- The Functional Assessment Questionnaire (FAQ; (also known as the Functional Activities Questionnaire)To explore the relationship between the treatment effects of E2609 on measured clinical efficacy scales (eg, MMSE, CDR) and its effects on CSF amyloid, CSF amyloid isoforms, brain amyloid, and vMRI
- To explore relationships between both E2609 dose and exposure, with PD and safety endpoints

# 9 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan

This study is a multicenter, placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild to moderate AD. (revised per Amendment 01)

A common set of inclusion criteria, consistent with the NIA-AA clinical research criteria for MCI due to AD or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study consists of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days, plus an additional window of up to 30 days if required [revised per Amendment 02]) will consist of a Screening Visit and a Baseline Visit. Screening assessments will be organized into 4 tiers; see Section 9.5.2.2, Table 6, and Figure 2.

All screening assessments must be completed, and eligibility to continue to the Baseline Period confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

All subjects (MCI/Prodromal and mild to moderate AD) will be randomized 1:1:1:1 to 4 treatment groups (5, 15, or 50 mg E2609 or placebo) (revised per Amendments 01 and 05)

An overview of the study design is presented in Figure 1.

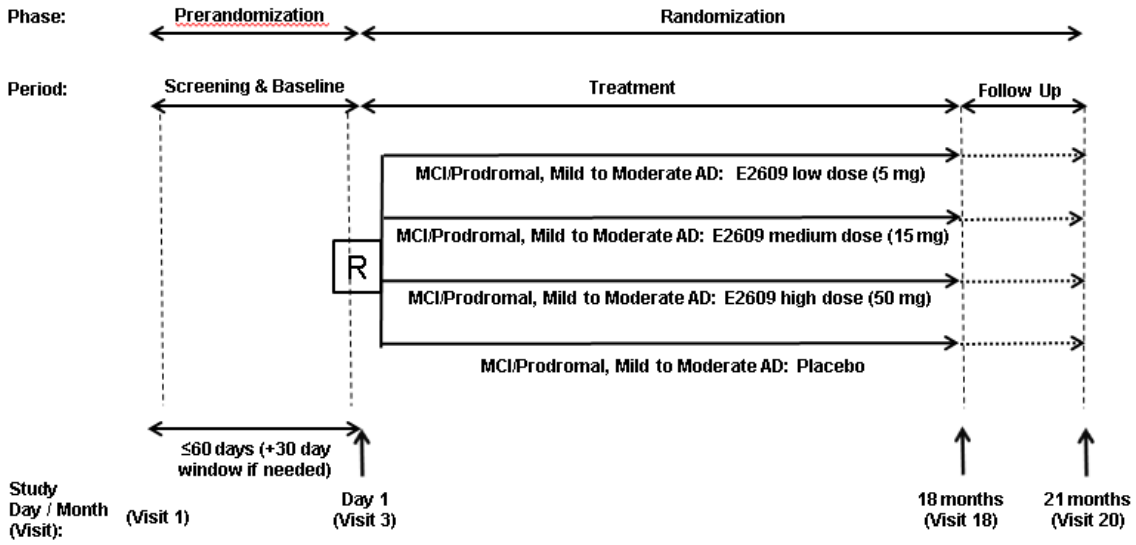



**Figure 1 Design of Study E2609-G000-202**

**(revised per Amendments 01, 02, and 05)**

R = randomization, AD = Alzheimer's Disease, MCI = mild cognitive impairment.

This study will be limited to approximately 35 sites in the United States, with approximately 60 (±20%) eligible subjects randomized at Visit 3, 1:1:1:1 to 4 treatment groups within each clinical cohort. In addition to the placebo group, 3 doses of E2609 will be used to reduce CSF Aβ levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/PD modeling shows these doses should achieve these targets when administered QD with food and will be evaluated based on the 4-week (or later) assessment of CSF Aβ(1-x) from subjects who provide voluntary consent for CSF measurement (see Section 9.4.4 ). (revised per Amendments 01, 02, 04, and 05) Safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the 1st subject is randomized into the study, an independent DSMB (including at least 1 immunologist) will review all safety data in an unblinded manner. The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. (revised per Amendments 01, 04, and 05)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

Interim analyses of the E2609 plasma PK for all subjects and the E2609 CSF PK and PD profiles will be performed on baseline data and samples collected after at least 4 weeks of treatment. (revised per Amendment 05) Refer Section 9.7.3 for more detail. These data will be used to evaluate the CSF PD effects of E2609 doses, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels (see Section 9.4.4). The median and mean percentage

change from baseline in CSF Aβ(1-x) measured after 4 weeks or more of treatment for each dose of E2609 and the 90% confidence interval (CI) for the median will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline determined after at least 4 weeks of dosing. (revised per Amendments 01, 02, 03, and 04)

Once subjects have completed at least 12 weeks of treatment (or discontinued study drug early), an interim safety analysis will be conducted by Eisai and the DSMB. (revised per Amendments 01, 04, and 05) Subjects will continue study drug while the DSMB reviews all the available safety data. (revised per Amendment 05) At the time of this interim safety analysis, some subjects will have more than 12 weeks of safety data.

If there are safety signals with one of the E2609 dose groups that would require dose adjustment, changes to dose will be reflected in an amendment to the protocol. Similarly, if the interim PK/PD analyses demonstrate that further dose adjustment is required, changes to dose will be reflected in an amendment to the protocol. Information on how the data from these subjects will be handled in the statistical analysis will be described in the Statistical Analysis Plan. (revised per Amendment 04)

Interim analyses are planned and are discussed in Section 9.7.3. (revised per Amendment 03)

### 9.1.1 Prerandomization Phase

The Prerandomization Phase includes a Screening Visit and a Baseline Visit. All Screening Visit assessments must be completed and eligibility to progress must be confirmed before any Baseline Visit assessments are performed. All Screening Visit and Baseline Visit assessments must be completed within 50 days (plus an additional window of up to 30 days if required [revised per Amendment 02]) and a window of no more than 10 days is to be observed between the completion of all Baseline Visit assessments (including confirmation of eligibility following all Baseline Visit assessments) and randomization into the study at Visit 3 (revised per Amendment 02). Thus, the Prerandomization Phase will last for up to 60 days, plus an additional window of 30 days if required (revised per Amendment 02). The series of assessments conducted during this phase will determine eligibility for randomization into the study.

Inclusion criteria are discussed in Section 9.1 and detailed in Section 9.3.1. Before randomization, the clinician will provide a judgment on the classification of a subject as either MCI/Prodromal or likely mild to moderate AD. (revised per Amendment 01) This judgment may be discussed and reviewed with the Sponsor or Sponsor's representative, as necessary.

Results of the Screening safety magnetic resonance imaging (MRI) will be valid for 90 days from the date of scanning. Results of the lumbar puncture (LP) from subjects who voluntarily consent for CSF measurement will be valid for 90 days from the date of testing. Results of Screening PET scans conducted specifically for this study and for use in the

longitudinal analyses will also be valid for 90 days from the date of scanning. These assessments will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. Historical PET scans used for determination of eligibility only (ie, not used for the longitudinal analyses) are valid for 12 months. (revised per Amendment 02)

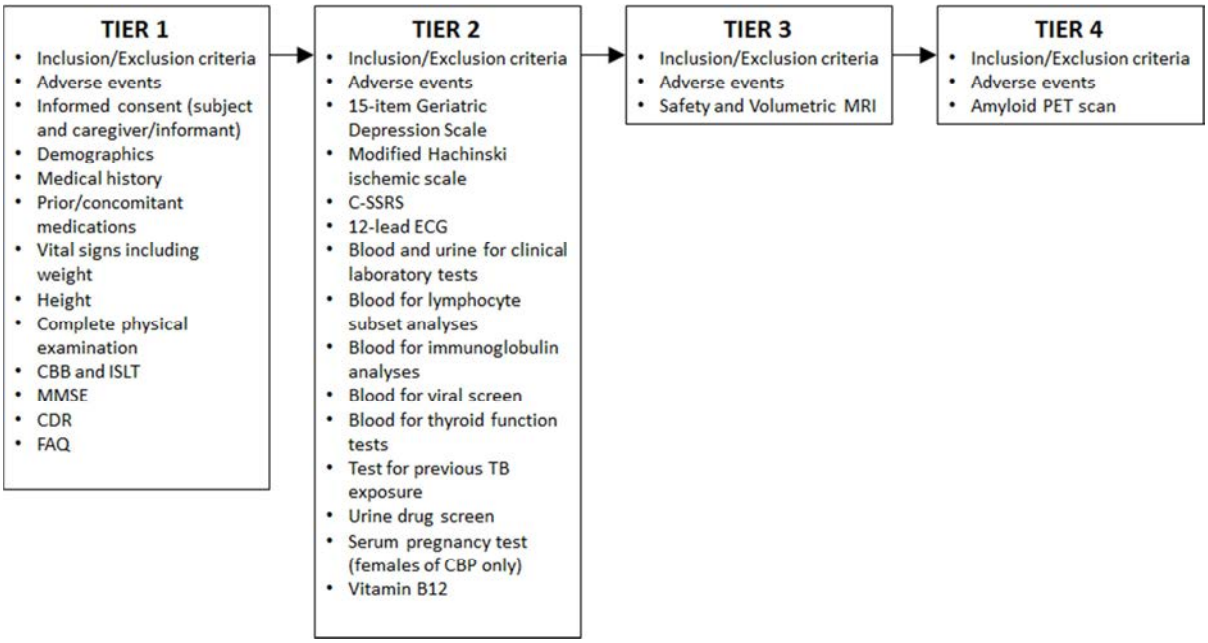
#### 9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and caregiver or informant, and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained from both the subject and the caregiver or informant. The caregiver or informant needs to be present at this visit.

Study site personnel will interview the subject and caregiver or informant to obtain demographic and clinical information as described in Table 6, and will review inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2 and perform any required assessments in order to complete these criteria. Prior medications and medications currently being taken by the subject will be reviewed (see Section 9.4.7). The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

Clinical assessments for eligibility will be conducted during the Screening Visit as described in Table 6 and Figure 2.

Every effort should be made to conduct these assessments in the morning, but if this is not possible, they should be conducted at the same time of day at all subsequent visits. The screening assessments/procedures have been organized into 4 distinct tiers (Table 6 and Figure 2). All assessments/procedures in each tier should be completed, and eligibility to continue screening in the study confirmed, before any assessments/procedures from the next tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures as long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. (revised per Amendment 01)




## Figure 2 Assessments to be Performed at Screening by Tier

CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), ISLT = International Shopping List Task (immediate and delayed recall), MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PET = positron emission tomography, TB = tuberculosis.

Cognitive assessments (Tier 1) are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). The recommended order of assessments at Screening is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. (revised per Amendment 02) The investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session (Tier 3).

Amyloid PET imaging will be used to confirm all subjects have amyloid deposition in the brain (Tier 4). An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. If an historical amyloid positive PET scan is being used, it should be submitted to the central PET reading group after the subject has completed and passed all Tier 1 assessments. (revised per Amendment 02)

#### 9.1.1.2 Baseline Period

All Screening Visit assessments must be completed (and eligibility to progress confirmed) before any Baseline Visit assessments are performed. The Baseline Visit assessments (per Table 6 and Section 9.5.1.2) are to be completed as soon as possible after completion of the final Screening Visit assessment (ie, PET scan) such that all Screening Visit and Baseline Visit assessments are completed within 50 days, plus an additional window of up to 30 days if required. (revised per Amendment 02)

Inclusion and exclusion criteria will again be reviewed, vital signs including weight will be recorded, and a 12-lead ECG will be conducted in triplicate. A routine physical examination will be conducted and a dermatological assessment and neurological examination (including the Brief Smell Identification Test [Sensonics Inc.]) will be performed. (revised per Amendment 04) A urine pregnancy test will be conducted for females of childbearing potential. Blood will be collected from all subjects for clinical chemistry and hematology, lymphocyte subset analyses, Ig analyses, and PD assessments. Blood samples will be collected and stored for determination of a subject's previous exposure to infective pathogens in the event of AEs that warrant further investigation occurring at a later point in the study. Psychometric assessments will be administered to the subject in the order stated in Table 6. The caregiver or informant needs to be present at this visit. The Columbia Suicide Severity Rating Scale (C-SSRS) will also be administered (Section 9.5.1.5.11).

For subjects who consent to CSF sample collection, a CSF sample will be obtained at this visit for PK and PD assessments (see Section 9.5.1.4). (revised per Amendment 02)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

Blood will be collected from all subjects for pharmacogenomic (PGx) analyses of apolipoprotein E (*ApoE*) and the N-acetyltransferase 2 (*NAT2)* phenotype of subjects enrolled in the study (see Section 9.7.1.7.2).

### 9.1.2 Randomization Phase

Subjects who complete the Baseline Visit assessments, and are eligible based on the inclusion and exclusion criteria (see Section 9.3.1 and Section 9.3.2), will begin the Randomization Phase no more than 10 days after completion of the Baseline Visit assessments and confirmation of the eligibility of the subject based on the results of all the Baseline Visit assessments (revised per Amendment 02).

The Randomization Phase will consist of a Treatment Period of 78 weeks duration and a Follow-Up Period of 12 weeks after the last dose of study drug.

#### 9.1.2.1 Treatment Period

Subjects will be randomized at the beginning of the Treatment Period and will receive study drug or placebo, to be administered orally QD with food. Double-blinding to study drugs will be in effect throughout the Treatment Period. The dose for a subject will not be changed during the study. (revised per Amendment 05)

Safety criteria for discontinuation of study drug are detailed in Section 9.3.3.

Subjects will attend the study site every week for the first 4 weeks after beginning study drug, then fortnightly until 12 weeks have elapsed since first dose. Visits will then be conducted at 16, 20, 26, 39, 52, 65, and 78 weeks after the first dose.

#### 9.1.2.2 Early Discontinuation

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug. (revised per Amendments 04 and 05)

#### 9.1.2.3 Follow-Up Period

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 4 posttreatment Follow-Up Visits: 2, 4, 8, and 12 weeks after the last dose of study drug. If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the post-treatment Follow-Up Period. (revised per Amendment 04)

The end of the study will be defined as the date of the clinical database lock (ie, when all study data are collected and data validation is completed).

As required by some regulatory agencies, the following estimates are provided:

- The study will begin in Nov 2014 and is projected to end by Apr 2018. (revised per Amendment 05)
- The maximum estimated period for each subject on study is anticipated to be approximately 2 years.

## 9.2 Discussion of Study Design, Including Choice of Control Groups

### 9.2.1 Overview

The primary objective of the study is to assess the safety and tolerability of daily dosing with E2609 in subjects with MCI/Prodromal AD and in subjects with mild to moderate AD. Immunological and hematological parameters will also be assessed. (revised per Amendment 04)

The inclusion criteria for the MCI/Prodromal cohort will be consistent with the NIA-AA criteria for MCI due to AD (Albert, et al., 2011) and with the definition of Prodromal AD per Dubois et al., 2010 (see Section 9.2.2).

There is no active or positive control for this study as at this time, there is no cure for AD, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

Secondary endpoints include CSF PK and plasma PK parameters of E2609 based on population PK analysis and the percentage reduction of Aβ(1-x) and Aβ(1-42) in CSF relative to baseline from 4 weeks and up to 18 months of treatment. The intrinsic and extrinsic factors on the PK characteristics will also be explored.

Exploratory endpoints include CSF Aβ(1-40) and BACE1 measures as well as CSF biomarkers of neuronal degeneration (eg, t-tau and p-tau), volumetric MRI measurements, plasma amyloid measurements, brain amyloid levels as measured by amyloid PET and clinical assessments. (revised per Amendment 05) Exploratory endpoints including assessments of efficacy, safety, and other biomarkers are also included.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups (Section 9.7.4) Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

The rationale for the selection of doses used in the study is provided in Section 9.4.4.

### 9.2.2 Rationale for Study Population

By the time AD progresses to dementia, with loss of functional capabilities, the amyloid load in the brain is approaching a plateau and significant neurodegeneration has occurred (Jack, et al., 2010). Consequently, there is a growing view within the AD field that it may be necessary to initiate disease modifying treatments earlier, before the onset of clinical dementia (Aisen, et al., 2010). However, this hypothesis remains to be demonstrated with clinically effective therapies, and may not apply to all therapeutic classes, it is possible that this consideration explains the failure of the humanized monoclonal antibody bapineuzumab (which targeted brain amyloid) to demonstrate clinical efficacy in late-phase studies in mild to moderate AD dementia. (revised per Amendment 01)

With this consideration taken into account, the primary clinical population of focus in this study is subjects with MCI/Prodromal AD. The mechanism of action of a BACE1 inhibitor where amyloid production is reduced means E2609 is more likely to be efficacious (ie, slow disease progression) the earlier in disease progression treatment is started, where limited neurodegeneration has occurred and associated clinical deficits are at a minimum. However, since the effect of BACE1 inhibition along the AD continuum remains to be characterized, E2609 will also be evaluated for its profile in mild to moderate stages of AD, in the event

data emerge supporting its use beyond MCI/Prodromal AD. Indeed, recent data support the notion of continued progression of amyloid pathology even in these later stages of the disease (Hu, et al., 2015), although at a slower pace, suggesting a positive effect of BACE inhibition and amyloid beta reduction cannot be ruled out even in the later stages of the disease trajectory. Hence, in this study, E2609 will be assessed in subjects with disease states ranging from MCI/Prodromal to mild and even moderate AD. (revised per Amendment 01)

As discussed, efficacy is more likely to be observed in subjects with MCI/Prodromal AD but there is the possibility that efficacy will also be evident following administration of an amyloid modifying agents such as E2609 in subjects with more advanced disease such as mild to moderate AD. (revised per Amendment 01) For example, a study of tarenflurbil, a selective Aβ(1-42)-lowering agent, on cognition and function in subjects with mild to moderate AD showed the subjects with mild AD had lower rates of decline than those in the placebo group in activities of daily living and global function; however, slowing of cognitive decline did not differ significantly (Wilcock, et al., 2008). Similarly, differential effects on cognitive measures have been observed with solanezumab, where some benefit from treatment was observed in subjects with mild AD, although studies with solanezumab were considered to have failed to improve cognition or functional ability significantly (Doody, et al., 2014). Therefore, it is relevant to compare the effect of the BACE1 inhibitor E2609 in 2 different subject populations that differ in terms of AD severity before the initiation of large Phase 3 clinical studies. (revised per Amendment 01)

### 9.2.3 Rationale for Clinical Endpoints

The 14-item version of the ADAS-Cog will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007).

The CDR is a clinical global rating scale requiring the interviewing of both the subject and an informant who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975)

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al,. 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials on the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson et al., 2011, Lim, et al., 2012a, Lim, et al., 2012b). Data computations indicate

that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with E2609 treatment.

The CBB is a brief, computer-administered cognitive test battery that requires approximately 10 minutes for administration (Darby, et al., 2012; Fredrickson, et al., 2008; Maruff, et al., 2009). The CBB has been used to detect cognitive impairment in several neurodegenerative conditions including the measurement of cognitive function in healthy older adults and in adults with clinically diagnosed AD and prodromal AD (Darby, et al., 2009; Hammers, et al., 2012; Lim, et al., 2012a; Lim, et al., 2012b). The administration, scoring, and reporting of the CBB is automated and highly standardized, resulting in cognitive paradigms that have been well-validated in neuropsychological and cognitive studies (Fredrickson, et al., 2008; Maruff, et al., 2009). See Section 9.5.1.3.1 for further details.

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression. Volumetric magnetic resonance imaging is discussed in Section 9.2.4.4.

## 9.2.4 Rationale for Biomarkers

### 9.2.4.1 Overall Rationale

The biomarker strategy for this study includes the following aims:

- To establish an amyloid load in the brain at study entry (via the PET eligibility inclusion criterion)
- To evaluate safety (principally by MRI)
- To evaluate a PD effect in terms of both Aβ in CSF and brain amyloid assessed by amyloid PET and to establish that this PD effect is maintained long-term (revised per Amendment 02)
- To evaluate disease modification through longitudinal assessments of vMRI, amyloid PET, and CSF biomarkers of neurodegeneration (t-tau and p-tau)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

### 9.2.4.2 Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect of E2609 on Aβ(1-40) +Aβ(1-42) and other C-terminally truncated Aβ peptides such as Aβ(1-38) through inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using [$^{11}$C]PiB, suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain

parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases in CSF Aβ concentrations that are seen in AD are believed to be related to this decrease in brain Aβ availability.

Both t-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni and Bhaskar, 2012). CSF tau measurements have been correlated with cerebral atrophy, while their ratios with Aβ42 have provided useful predictors of cognitive decline and progression to dementia due to AD. Rebalancing dysregulated amyloid production early in the process may positively affect the neurodegenerative process and thus affect these markers and benefit the disease trajectory. Therefore, monitoring these markers in conjunction with amyloid imaging may provide further supportive evidence of disease modifying effects. (revised per Amendment 04)

Baseline levels of Aβ(1-42), t-tau, and p-tau will also help elucidate the extent of AD pathology at entry to the study and can be combined with baseline levels of *ApoE4* genotyping in addition to the baseline imaging variables to help explain differences in treatment response.

The study will be stratified at randomization for *ApoE4* gene status in order to account for any *ApoE* status by treatment interaction or *ApoE* status by amyloid-related imaging abnormalities risk interaction.

#### 9.2.4.3 Amyloid PET

Amyloid PET imaging will be used in this study for 2 primary reasons: 1) to confirm the presence of AD pathology in the brain of subjects with MCI/Prodromal AD or mild to moderate AD at entry to the study; and 2) to evaluate the effects of E2609 on amyloid levels in the brain, both by whole brain analysis (the average of 5 to 6 cortical regions) and brain region analysis. (revised per Amendment 01)

Longitudinal amyloid PET imaging will be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug) as an exploratory measure of the potential disease-modifying effects of E2609. Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses). (Revised per Amendments 02 and 05)

#### 9.2.4.4 vMRI

Volumetric imaging will be used to evaluate the effects of E2609 on rates of atrophy across the different dose groups and to provide support that effective treatment is associated with modification of disease course (secondary endpoint for the MCI/Prodromal population and exploratory endpoint for the mild to moderate AD population). (revised per Amendment 01) A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the

brain (frontal cortex) in its later stages. Clinically efficacious doses are predicted to be associated with a slowing in the rate of hippocampal atrophy compared with rates observed in the placebo and non-efficacious dose groups. Treatment effects on left and right hippocampal, whole brain, and total ventricular volumes are exploratory endpoints.

Annualized rates of change of 2% to 3% have been reported for the AD brain compared with 1% in MCI and <1% in age-matched controls (Hua, et al., 2010, Leung, et al., 2010). However, subjects with MCI due to AD-dementia (CSF Aβ <192 pg/ml or positive amyloid imaging) show rates of atrophy comparable to those observed in subjects with AD-dementia (Hua, et al., 2009; Hua, et al., 2010; Leung, et al., 2010; Morra, et al., 2009), supporting the notion that such subjects are on similar trajectories as those with mild AD-dementia. Lower levels of CSF Aβ42, amyloid positivity on PET imaging, and higher levels of CSF t-tau in addition to the presence of the *ApoE4* allele have all been associated with greater rates of brain atrophy (Fjell, et al., 2010a; Fjell, et al., 2010b) and will be entered as covariates in various analyses. Hippocampal atrophy has also been shown to predict clinical progression independently of amyloid levels in the brain (Jack, et al., 2010), and this measure will be entered as a covariate in the analysis of the clinical endpoints along with the aforementioned variables.

Brain volume (total ventricular volume, whole brain, temporal lobe) generally shows a modest correlation with performance on a number of cognitive scales (Hua, et al., 2009; Hua, et al., 2010; Freeborough, et al., 1997; Leung, et al., 2010). Using volumetric analysis performed at 6-month intervals, these relationships and the effects of E2609 treatment will be explored further. Recent advances in analysis software have made structural imaging more sensitive to detect small changes and able to reliably measure rates of atrophy at these intervals, particularly in the posterior parietal and the lateral temporal regions during the early stages of disease (Hua, et al., 2009; Hua, et al., 2010). Given these observations, a demonstration of significant slowing or stabilization in the rate of atrophy in response to treatment, compared with placebo, will offer further support for disease modification.

### 9.2.5 Clinical Risks and Mitigation Strategy

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, and to mitigate clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. These safety aspects include the following:

- Immunology-related and infection-related exclusion criteria
- Review of unblinded safety data by an independent DSMB at regular intervals
- Safety criteria for discontinuation of study drug based on CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cell) and other lymphocytes (absolute counts and percentage change from baseline), skin rash, reoccurrence of herpes virus infections including any oral herpes, genital herpes or shingles, other infections, MRI changes, ECGs, and pregnancy.

In addition to the features above, other safety aspects of this study designed to mitigate clinical risk include the following:

- Blinded safety data will be monitored by Eisai at regular intervals during the course of the study
- Routine safety assessments will include the monitoring and recording of all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events. To assess potential immunomodulatory effects, peripheral blood mononuclear cells (PBMCs) will be collected at baseline, during treatment, and post-treatment.

As per the communication from the Food and Drug Administration (FDA) in Aug 2013, there are concerns that hypopigmentation of the skin and mucous membranes may occur with BACE1 inhibitory drugs. Although no such effects have been seen with E2609 to date, assessments by a reviewing dermatologist will be performed at regular intervals during the study. These assessments will be made centrally, using standardized photography and will

specifically include evaluation of any areas of depigmentation or any rash. Dermatological assessments will be supplemented with a specific question to subjects regarding skin changes at each visit. Any such changes could be referred to the central reviewing dermatologist, and to a local dermatologist if needed, for further evaluation. See Section 9.5.1.5.8 for further details.

- Baseline and on-study blood and DNA samples will be taken and stored for all subjects, and CSF samples will be taken and stored for all subjects who consent to CSF sample collection (revised per Amendment 02). These samples may be tested in the event that a subject develops AEs that warrant further investigation (eg, if a subject develops a treatment-emergent infection) (see Section 9.5.1.2.2).
- Central reading of safety brain MRI assessments (including any MRI evidence of demyelination) will be performed at Screening, at approximately 6-month intervals during the Treatment Period, and at the final Follow-Up Visit.
- Full neurologic examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. Details of the neurologic examination are given in Section 9.5.1.5.9.
- Cognitive decline will be assessed as a safety assessment (ADAS-cog$_{14}$, MMSE, and CBB). Of particular importance will be the assessment of reaction time testing using the detection and identification tasks on the CBB.
- An assessment of suicidality using the C-SSRS will be performed at Screening, Baseline, and at regular intervals during the Treatment and Follow-Up Period (see Section 9.5.1.5.11).
- All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will have at least 4 off-treatment Follow-Up visits (2, 4, 8, and 12 weeks after the last dose of study drug). More frequent safety assessments can be made as unscheduled assessments/visits during the off-treatment Follow-Up period, if clinically indicated. (revised per Amendment 04)
- An ophthalmic examination will be conducted at Baseline and if the subject experiences visual disturbances during the course of the study (see Section 9.5.1.2.1).

## 9.3 Selection of Study Population

Approximately 60 (±20%) eligible MCI/Prodromal or mild to moderate AD subjects will be randomized at approximately 35 sites in the United States (revised per Amendments 02 and 04). There will be no restriction to the number of subjects from either population.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

### 9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD (Albert, et al.,

2011) or AD dementia (McKhann, et al., 2011) and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at Screening Visit 1:**

(revised per Amendment 02)

a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation

b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT. Alternatively, cognitive impairment of at least 0.5 SD from age-adjusted norms in delayed recall on the ISLT plus impairment of at least 1 SD from age-adjusted norms in at least 1 other computerized learning and memory test (ISLT immediate recall, or 1 of the learning and memory components of the CBB). (revised per Amendment 02)

c. FAQ ≤24 (revised per Amendment 01)

d. MMSE ≥16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading; an historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group (revised per Amendment 02)

3. Male or female, age 50 to 85 years, inclusive at time of consent

4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.

5. If receiving acetylcholinesterase inhibitors (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the Baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.

6. Must have been on stable doses of all other permitted chronically used concomitant

medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization

### 9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or MRI
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and <1cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could, in the opinion of the investigator, confound the MCI/Prodromal or mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendments 01 and 02)
7. A score of ≥8 on the 15-item Geriatric Depression Scale (GDS) at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the LLN for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices

other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.

12. Any contraindications to LP for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity). Only applicable to subjects consenting to CSF sample collection (revised per Amendment 02)
13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of Ig deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization.
20. Any active infection within the last 4 weeks prior to randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below population-adjusted LLN at Screening or Baseline and confirmed by a repeat test conducted 1 week after the initial test. The population-adjusted LLN for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are 396, 157, and 74 cells/μL respectively. See Appendix 5. (revised per Amendment 02)
23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the Investigator and the Medical Monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of clinical immunodeficiency. The discussion with the Medical Monitor should include a

detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)

24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate ECGs. A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute (bpm) at Screening or Baseline
29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.
33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo). Diagnosis of an underlying disease causing hypopigmentation is not necessary for exclusion if the clinical presentation is consistent with such a condition. Hypopigmentation associated with scarring need not be exclusionary. (revised per Amendment 02)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the C-SSRS suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before

Screening

37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period or for 28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.
    - Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
    - (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]). (revised per Amendment 04)

### 9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may discontinue study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to stop study drug or withdraw from the study at any time for any reason.

Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). Follow-Up Visits will also be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug (see Section 9.1.2.3). (revised per Amendments 04 and 05)

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the Subject Disposition eCRF page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study drug and withdraws from the study at the same time, the ED Visit will be followed (see Section 9.5.5).

Safety-related criteria for discontinuation of study drug include the following:

a. A study drug discontinuation threshold will be set based on absolute counts of CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells). The discontinuation threshold will be set at below the level of the population-adjusted LLN (CD4=396 cells/µL; CD8=157 cells/µL; and CD19=74 cells/µL), at a level that represents a greater risk of opportunistic infection in the treated population. (revised per Amendment 02) For CD4 (T helper cells) the discontinuation threshold is 250 cells/µL. For CD8 (cytotoxic T cells) and CD19 (B cells) the discontinuation thresholds are 150 cells/µL and 50 cells/µL, respectively. Any subject who has CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below the discontinuation threshold as confirmed by a repeat test conducted within 1 week of the initial test but who has no clinical signs or symptoms of infection, will have study drug temporarily suspended for at least 2 weeks but no more than 4 weeks. During this period of study drug suspension, lymphocyte subset counts and complete blood count (CBC) with differentials will continue to be tested weekly until CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) have all returned to greater than the population-adjusted LLN after which time study drug can be resumed. Testing of lymphocyte subset counts and CBC with differentials is required weekly for 4 weeks following resumption of study drug administration. Temporary suspension and rechallenge with study drug is only permitted once for any given subject. If the lymphocytes and CD counts do not return to greater than the population-adjusted LLN within 4 weeks from the start of temporary suspension the subject will need to be permanently discontinued from study drug. (revised per Amendment 04)

b. Subjects with CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between the population-adjusted LLN and the discontinuation threshold will have lymphocyte subset counts performed on a weekly basis. (revised per Amendments 02 and 04) During the early stages of the treatment period, where visits are conducted weekly (ie, Visits 4, 5, 6, and 7), lymphocyte subsets are already scheduled to be

measured on a weekly basis and so additional visits or blood draws are not required. (revised per Amendment 02) For these subjects, the decision as to whether the subject remains on study drug or is to be discontinued from study drug will be based upon clinical judgment and will take into account any clinical presentation in addition to the lymphocyte subset counts. These subjects may continue with treatment if there is no clinical evidence of infection. They will be discontinued from study drug if they have infections of a moderate to severe intensity (eg, subjects whose infections are not localized, or are systemically unwell, or who require systemic anti-infective drug treatment).

**Table 1 Study Drug Actions for Lymphocyte Subset Absolute Counts**

| Lymphocyte subset absolute counts | Action | Decision to continue, discontinue, or temporarily suspend study drug |
|---|---|---|
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold and no clinical signs or symptoms of infection | Retest within 1 week along with<br>CBC with differentials | If retest performed within 1 week confirms lymphocyte subset counts below the discontinuation threshold, temporarily suspend study drug for between 2 and 4 weeks. Continue weekly testing of lymphocyte subsets and CBC with differentials. Rechallenge with study drug allowed when CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts all greater than population-adjusted LLN. Temporary suspension and rechallenge permitted only once for each subject. |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between population-adjusted LLN and discontinuation threshold | Lymphocyte subset counts (and CBC with differentials) to be performed weekly until lymphocyte subset counts return to ≥ population-adjusted LLN | Decision will be based upon lymphocyte subset counts and clinical judgment |

LLN = lower limit of normal, CBC = complete blood count.

(Table revised per Amendments 02 and 04)

c. Subjects with clinical evidence of infection will have their CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts measured. Blood and other biological samples will also be collected for investigations of infective pathogens (eg, serological tests, quantitative polymerase chain reaction, microscopy, and culture) where appropriate. In subjects with infection, if any of their absolute cell counts meets the discontinuation thresholds, study drug will be discontinued. All subjects with severe infections will be discontinued from study drug. All subjects with herpes zoster

(shingles) or ocular herpes infections will be discontinued from study drug, regardless of severity of presentation. Subjects with mild or moderate infection may continue treatment with study drug unless otherwise clinically indicated or otherwise specified below. Specifically, when any of the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are between the population-adjusted LLN and the discontinuation thresholds, subjects with infections of moderate intensity will be discontinued from study drug (eg, subjects whose infections are not localized, or subjects who are systemically unwell, or who require systemic anti-infective drug treatment). All subjects with infection who are discontinued from study drug will be followed for a period of 12 weeks or until the infection resolves/ stabilizes or until the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts have returned to greater than population-adjusted LLN (whichever comes latest). (revised per Amendments 02 and 04)

**Table 2 Study Drug Actions for Lymphocyte Subset Absolute Counts and Infection**

| Criterion | Severity of Infection | | | |
|---|---|---|---|---|
| | None | Mild | Moderate | Severe |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold | If confirmed with repeat testing within 1 week, then temporarily suspend study drug as per instructions above. | Discontinue study drug | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between population-adjusted LLN and discontinuation threshold | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts always > population-adjusted LLN | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated (See (e) for exception) | Discontinue study drug |

LLN = lower limit of normal.

(Table revised per Amendments 02 and 04)

d. A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (see (e) for exception), will be discontinued from study drug and a dermatological consult will be requested regardless of whether the rash is considered drug-related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study

drug, a dermatological consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

e. Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

f. Development of any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. If discontinued from study drug, subjects will undergo an ED Visit within 7 days after discontinuation and will attend the Follow-Up Visits 2, 4, 8, and 12 weeks after the last dose of study drug. They will also undertake an Unscheduled Visit (with MRI) at approximately 4 weeks after the visit at which such MRI features were first identified. An MRI will also be performed at approximately the time of the final Follow-Up Visit (Visit 20). Additional visits for safety may be arranged if clinically indicated in the opinion of the investigator, including after 12 weeks after the last dose of study drug. At any time during the treatment period, subjects who have asymptomatic, treatment-emergent microhemorrhages as detected by MRI, but none of the features which merit discontinuation of treatment (ie, vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic treatment-emergent microhemorrhage) may continue with treatment. These subjects will have safety assessments (including MRI) at approximately 4 weeks after the visit at which such MRI features were found. They will also continue with the scheduled MRI scans. Additional unscheduled MRI scans may be arranged on an individual subject basis in discussion with the study medical monitor. (revised per Amendment 04)

g. A postdose ECG with an average QTcF interval >500 msec from triplicate ECGs

h. A postdose ECG with a QTcF interval increase from baseline >60 msec and a QTcF interval >450 msec as demonstrated from triplicate ECGs

i. Any seizure (motor or non-motor)

j. Pregnancy

## 9.4 Treatments

### 9.4.1 Treatments Administered

For this study the test drug is E2609 and the control drug is placebo. All study drugs are to be administered orally, QD, with food.

Treatments to be administered are 5, 15, and 50 mg E2609 or placebo as shown below and in Figure 1. (revised per Amendments 01 and 05) Study treatment will begin on Day 1 (at the study site) following Randomization and will continue for approximately 78 weeks. Please refer to Table 7 and Section 9.5.1.4.1 for specific information on drug administration on days when PK sampling is to be performed.

Study drug doses will remain the same for each individual subject unless the interim PK/PD analysis determines that an entire dose level requires adjustment (Section 9.4.4). See Section 9.3.3 for safety-related discontinuation criteria of study drug. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

### 9.4.2 Identity of Investigational Product

E2609 tablets of 5-, 10-, and 25-mg dose strengths will be supplied. Placebo tablets of identical appearance will also be available. Each subject will receive 2 tablets, which combined will make up the required doses of E2609 5, 15, 50 mg, or placebo. The tablets will be supplied by the Sponsor in labeled blister packs. The product release certificates for E2609 and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either E2609 or placebo, or both (see Section 9.4.2.3 for labeling details).

#### 9.4.2.1 Chemical Name and Formula of E2609

- Test drug code: E2609
- Generic name: not applicable
- Chemical name: International Union of Pure and Applied Chemistry
- *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

#### 9.4.2.2 Comparator Drug

Not applicable.

#### 9.4.2.3 Labeling for Study Drug

E2609 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only

- Name and address of the sponsor
- Chemical name/drug identifier (ID)
- Lot number/batch number
- Storage conditions, expiration date if necessary

#### 9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

### 9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups are described in Section 9.4.1. (revised per Amendments 01 and 05)

Randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized blister card identification numbers. At enrollment, the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 3), the IxRS will assign each subject a unique randomization number.

### 9.4.4 Selection of Doses in the Study

It is not known how the level of CSF or brain Aβ reduction is related to clinical efficacy. Therefore, in this study, doses will be selected such that at steady state, they will result in 25%, 50%, and 75% reduction in CSF Aβ levels from baseline to cover a broad range of PD effects.

In Study 007, the relative bioavailability of a tablet formulation of E2609 in the fed and the fasted states compared with the capsule formulation in the fasted state (used in Studies 001 and 002) was investigated. It was found that when the tablet form of E2609 (50 mg) was administered with food, the exposure (ie, AUC) of the parent drug E2609 was higher, with lower maximum observed concentrations and reduced exposure to the metabolites, compared with either formulation in the fasted state.

Based on the PK/PD modeling using data from healthy volunteer Studies 001, 002, and 007, doses of 5, 15, and 50 mg QD administered as the tablet formulation with food in this study should achieve CSF Aβ reduction from baseline of approximately 25%, 50%, and 75% at steady state, respectively (Table 3).

**Table 3 Predicted Steady State Plasma PK Parameters and CSF Amyloid β Reduction From Baseline**

| E2609 Tablet Daily Dose (mg) With Food | E2609 Plasma $C_{max,ss}$ (ng/ml) | E2609 Plasma $C_{ss,av}$ (ng/ml) | E2609 Plasma $AUC_{(0-24h)ss}$ (ng.h/ml) | % Reduction CSF BACE1 Activity | % Reduction CSF Aβ(1-x) |
|---|---|---|---|---|---|
| 5 | 6.2 | 3.3 | 80.3 | 16.2 | 33 |
| 15 | 18.6 | 10 | 240.9 | 36.6 | 56 |
| 50 | 62.1 | 33.5 | 803.0 | 65.7 | 79 |

Aβ(1-x) = amyloid beta monomer from amino acid 1 to x, $AUC_{(0-24h)ss}$ = area under the concentration x time curve at steady state from time zero to 24 hours, BACE1 = beta-amyloid converting enzyme, CSF = cerebrospinal fluid, $C_{ss,av}$ = average steady-state concentration, $C_{max,ss}$ = maximum plasma concentration at steady state, PK = pharmacokinetics.

The PK/PD modeling described above, which was conducted using data obtained from healthy volunteers, has also been supported by modeling of data from subjects with an underlying AD pathology (Study 101). Furthermore, external data with another BACE1 inhibitor (MK-8931) showed a similar PD effect in AD patients as in healthy volunteers (Forman, et al., 2013). Therefore we are confident that the modeling of E2609 effects in healthy subjects will be applicable for both MCI/Prodromal and mild to moderate AD dementia patients. (revised per Amendment 01)

The exposure of the highest dose in this study (50 mg QD tablet administered with food) is less than that of the 100 mg QD dose (capsule administered fasted) in Study 002.

The 100 mg QD dose administered for 14 days in Study 002 was well tolerated with no clinically significant changes in laboratory parameters, vital signs, or ECG parameters. On Day 15, for the 100 mg QD cohort in Study 002, there was a reduction of CD4 lymphocyte counts compared with placebo (CD4 lymphocyte counts on E2609 decreased by 3.1% from baseline, whereas the placebo control showed an increase of 8.7%), but this decrease was less than that observed at doses of 200 mg (22.9% decrease) or 400 mg (17.3% decrease). No subject had infections or drug rash while receiving E2609 100 mg QD or at lower doses in Study 002, whereas at 200 and 400 mg QD, 4 subjects had symptomatic orolabial HSV1 relapses and 2 subjects at the highest dose had drug rash. The highest dose for Study 202 of 50 mg QD (tablet administered with food) is therefore expected to have a similar or better safety profile compared with the 100 mg QD capsule (administered fasted) in Study 002. Specific exclusion criteria, blinded and unblinded safety monitoring procedures, and safety criteria for discontinuation from study drug are included in this study in order to mitigate any immunology-related risk with E2609, particularly in light of the progression from 14 days of dosing (Study 002) to 18 months of dosing in this study.

Interim analyses of the E2609 plasma PK for all subjects and the E2609CSF PK and PD profiles will be performed on baseline data and samples collected after at least 4 weeks of treatment. These interim analyses, as well as analyses of safety data, will be performed on an ongoing basis. Refer Section 9.7.3 for more detail. The median and mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment for each dose of E2609 and its 90% confidence interval for the median will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD

data and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline after at least 4 weeks of dosing. (revised per Amendments 01, 02, 03, 04, and 05)

### 9.4.5 Selection and Timing of Dose for Each Subject

E2609 is administered orally, QD, with food. Study treatment will begin on Day 1 following randomization and will continue for approximately 78 weeks.

### 9.4.6 Blinding

E2609 and placebo will be administered as tablets of identical appearance.

During the Randomization Phase and Follow-Up Phases, subjects, caregivers/informants, and all clinical site personnel involved with the conduct and interpretation of the study, including investigators will be blinded to the treatment codes (double-blind). In order to make decisions about the remainder of the study as well as the full E2609 clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. (revised per Amendment 03)

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (ie, those who are trained and certified to perform the various cognitive assessments that are undertaken in this study). Furthermore, at the site, the notes and reports relating to safety assessments must be kept separate from the notes and reports relating to efficacy, particularly for the CDR. (revised per Amendment 01)

Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

The PK/PD interim analyses will take place throughout the study as per Amendment 03 and will be conducted by an independent PK/PD scientist at the sponsor. Any additional changes to dose required for this study will be reflected in a further amendment to the protocol and the Statistical Analysis Plan will detail how data will be handled in the primary analysis. (revised per Amendments 02 and 04)

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

At the conclusion of the study, all unused drug supplies are to be returned to the Eisai approved contract packaging vendor.

### 9.4.7 Prior and Concomitant Therapy

Medication (including over-the-counter medications) or therapy administered to the subject before the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2. Prohibited medications are presented in Listing 1 through Listing 5. Medications that are permitted with restrictions are listed in 6 through Listing 8. (revised per Amendment 04)

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit: (revised per Amendment 04)

- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization. However, during the treatment period of the study, short term (not more than 14 days) use of steroids up to the equivalent of prednisolone 40 mg once daily is permitted after discussion with the Medical Monitor. Dosing with study drug should be suspended from the time steroid treatment is started. Complete blood count and lymphocyte subsets should be determined prior to starting steroid treatment and continue to be monitored weekly. Study drug may be resumed after discussion with the Medical Monitor when the following conditions are met: (1) treatment with steroids has been completed for at least 1 week; (2) total lymphocytes not <LLN; (3) no lymphocyte subsets are below the discontinuation threshold; (4) the investigator considers that the medical condition which required treatment with steroids has improved or resolved. Weekly testing of lymphocyte subset counts and CBC with differentials is required for 4 weeks following resumption of study drug administration. (revised per Amendment 04)

Subjects taking AChEIs or memantine must meet the following criteria in order to be included in the primary analyses:

- On a stable dose for 12 weeks before the Baseline cognitive assessments at Visit 2
- Remain on a stable dose while on study

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for any efficacy analyses. (revised per Amendment 05)

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed. Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before randomization. They may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 04)
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety, and are not prohibited above. (revised per Amendment 05)

Antiplatelet therapy: (revised per Amendment 04)

- For subjects who consent to CSF sample collection: Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) are permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.
- For subjects who do not consent to CSF sample collection: Aspirin and clopidogrel, individually or in combination, are permitted.

### 9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period. CRAs will review treatment compliance during site visits and at the completion of the study.

### 9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement

- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the principal investigator including a copy of the principal investigator's current medical license (required for United States sites) or medical registration number on the curriculum vitae
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the

designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

## 9.5 Study Assessments

### 9.5.1 Assessments

#### 9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

#### 9.5.1.2 Baseline Assessments

Assessments to be made at Screening and Baseline and throughout the study are described in Section 9.5.1.3, Section 9.5.1.4, and Section 9.5.1.5.

##### 9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, current medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment due to AD. Subjects will be asked about history of TB, infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV Types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include onset, duration, relapse frequency, severity, and treatments. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The 15-item GDS and modified Hachinski ischemic scale will also be assessed at Screening as part of the exclusion criteria.

Physical examinations (complete or routine) will be performed as designated in Table 6. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, and skin, and a neurological examination (including the Brief Smell Identification Test [Sensonics Inc.]). (revised per Amendment 04). A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### 9.5.1.2.2 VIRAL TESTING

As specified in Table 6, blood will be collected for screening for Hepatitis B and Hepatitis C for determining eligibility, and at Baseline for viral characterization.

#### 9.5.1.2.3 B12 TESTING

Blood will also be collected for vitamin B12 levels as specified in Table 6.

#### 9.5.1.2.4 TB EXPOSURE TESTING

Blood will also be collected for testing for previous TB exposure, as specified in Table 6.

#### 9.5.1.2.5 URINE DRUG TESTING

Urine will be collected for drug screening as specified in Table 6.

### 9.5.1.3 Efficacy Assessments

#### 9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

The timing of psychometric assessments is shown in Table 6 and Table 7. These assessments should be administered in the morning (or, if not possible, consistently at the same time of day) and should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). At the Screening Visit, the recommended order of assessments is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. At the Baseline Visit, the assessments are to be conducted in the following order: MMSE, CDR, ADAS-cog$_{14}$, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). (revised per Amendment 02)

At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

**Alzheimer's Disease Assessment Scale - cognitive subscale:** Discussed in Section 9.2.3. (revised per Amendment 05)

**Clinical Dementia Rating:** The CDR assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.**Mini Mental State Examination:** A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

**ISLT:** The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects will read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 15 minutes, in which time the CBB is performed, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

**CogState Brief Battery:** The CBB is a computer-based battery comprising 4 cognitive tests:

- Detection – a simple reaction time test where the subject presses a key when the card is turned face up from a pack of cards ("Has the card turned over"). Speed of response is the measure.
- Identification – a simple choice reaction time test where the subject presses 1 of 2 keys when the card just turned face up is either a red card or a black card ("Is the card red"). Speed of response is the measure.
- One Card Back – a simple working memory test where the subject presses 1 of 2 keys when the card turned face up is either the card seen in the immediately previous trial or not ("Is the previous card the same"). Accuracy of response is the measure.
- One Card Learning – a visual learning and memory test where the subject presses 1 of 2 keys depending on whether the card just turned face up has been seen before or not in the task ("Have you seen this card before in this task"). Accuracy of response is the measure.

**Functional Assessment Questionnaire:** The caregiver or informant provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent). (revised per Amendment 04)

#### 9.5.1.3.2 VOLUMETRIC MRI

Volumetric MRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the Alzheimer's Disease Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

Volumetric MRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. Volumetric MRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. Volumetric MRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 6 and Table 7, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

For subjects who consent to CSF sample collection, CSF samples will be collected by LP (gravity drip method) at the timepoints specified in Table 6 and Table 7 (revised per Amendment 02). The CSF sample taken at the Baseline Visit will only be performed after subjects consent to CSF sample collection, and after confirmation of an amyloid positive PET scan (revised per Amendment 02). See Section 9.5.1.4.2 for further details.

### 9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

#### 9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of E2609. For subjects who consent to CSF sample collection, CSF samples will be collected for the determination of E2609 concentrations. (revised per Amendment 02) Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with E2609.

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 6 and Table 7. Two PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visits 5, 11, 14, and 16, and 4 to 8 hours postdose at Visit 7 and Visit 18 (or at the ED Visit). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug with food at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or at the ED Visit) the PK blood sample should be collected shortly before or shortly after completing the LP. (revised per Amendment 01) Although the PK sampling procedures at the ED visit should follow those of Visit 18, in the event that study drug has already been discontinued prior to the ED visit, then no dosing will be conducted. However, a PK sample at trough (before LP) will be collected, followed by LP at approximately the same time as previous visits. A 2nd PK blood sample will be collected as close as possible in time to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

Blood will also be drawn where possible at the 1st report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

#### 9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

**Biomarkers**

Subjects who consent to CSF sample collection will be encouraged to stay at the site after completion of LP for medical observation (revised per Amendment 02). At Baseline, a CSF sample will be collected by LP (gravity drip method) after fasting (preferred), or at least 2 hours after the most recent meal (Section 9.5.1.3.3). The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 [or later postrandomization timepoint] and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. (revised per Amendment 04) At visits where cognitive tests are also performed, if the tests are to be performed on the same day, the LP must be performed after the cognitive tests have been completed and the subjects should rest and drink some fluid to hydrate before the LP. (revised per Amendment 01) The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. The CSF sample will be used for PD assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 levels and activity. (revised per Amendment 04)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to

postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The pre- and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendment 04) BACE1 levels will be measured using internally developed fluorescence resonance energy transfer and ELISA based assay(s). Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

The blood sample collected for PD analyses at Baseline should be collected on the same day shortly before or shortly after completing the LP at Baseline. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

At the Baseline Visit, blood samples will be collected and stored for determination of prior exposure to any suspected infective agents in the event that the subject develops treatment-emergent AEs that warrant further investigation (eg, treatment-emergent infection). For subjects who consented to CSF sample collection, CSF samples from the Baseline Visit will also be stored for the same purpose. (revised per Amendment 02) Testing may include, but not be limited to, serological tests, viral titer by quantitative polymerase chain reaction, or human leukocyte antigen genotyping.

Blood samples will be collected for PD assessments as specified in Table 6 and Table 7. See Section 9.5.1.4.2 for further details.

For all subjects, baseline and on-study blood samples, DNA samples, and any CSF samples collected from subjects who consent to CSF collection will be stored for up to 15 years. (revised per Amendment 02)

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

**Pharmacogenomics**

A blood sample will be obtained at Baseline and will be used to determine the *ApoE* genotype (homozygous or heterozygous E4 versus non-E4) and the *NAT2* phenotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response, safety, or PK of E2609. Details of which genotype / phenotype data will be applied to the analyses of efficacy, safety or PK will be discussed in the Statistical Analysis Plan.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the

development of AEs, or underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

**Amyloid PET**

An amyloid PET scan will be performed at Screening to confirm deposition of amyloid in the brain. An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02) Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses) (Table 6). (revised per Amendments 02 and 05) PET scanning will be performed with a locally approved Aβ imaging agent (eg, Amyvid). Descriptions and detailed instructions for all imaging can be found in the imaging manual.

Amyloid PET imaging is an exploratory measure of the potential disease-modifying effects of E2609.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, lymphocyte subsets, Igs, and urine values; periodic measurement of vital signs and ECGs; performance of physical and neurological examinations; centralized dermatological assessments; the C-SSRS; and safety MRIs as detailed in Table 6 and Table 7 will also be conducted. Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and post-treatment for exploratory immunomodulatory and immune-based analyses.

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (see Section 9.4.6). (revised per Amendment 01)

##### 9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E2609.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product,

whether or not considered related to the investigational product (Note: It is not necessary to report every sign or symptom as a separate AE if the overall disease [diagnosis] is being reported as an AE.)

- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, discontinuation of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 20, as shown in Table 7). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF. SAEs will be collected for 3 months after the last dose of study drug, ie, through to the final Follow-Up visit (Visit 20). However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures. (revised per Amendments 04 and 05)

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the ADAS-cog$_{14}$, MMSE, ISLT and CBB (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 4.

- Euphoric mood
- Elevated mood

- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis
- Dissociative state

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.11 for a description of the C-SSRS).

The following AEs will require the collection of information sufficient to provide a detailed description of the event, treatment and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection; any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a "yes" answer to Type 4 or 5 suicidal ideation, or a "yes" response to any suicidal behavior on the C-SSRS.

All AEs must be followed through the final Follow-Up visit (Visit 20), or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. (revised per Amendment 04)

**Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.**

### Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

| | |
|---|---|
| Mild | Discomfort noticed, but no disruption of normal daily activity |
| Moderate | Discomfort sufficient to reduce or affect normal daily activity |
| Severe | Incapacitating, with inability to work or to perform normal daily activity |

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

## Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

*Classification of Causality*

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

#### 9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reportable using the criteria of important medical event if the event does not meet other serious criteria: new onset seizures, ocular herpes.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the eCRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

#### 9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 4. Subjects should be in a seated or supine position during blood collection. Table 6 and Table 7 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

See Section 9.3.3 for safety criteria for discontinuation from study drug related to absolute counts of CD4, CD8, and B lymphocytes, and for lymphocyte subset counts.

## Table 4 Clinical Laboratory Tests

| Category | Parameters |
|---|---|
| **Hematology** | Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils).<br><br>PT, PTT, and INR (Screening and Baseline only) (revised per Amendment 02) |
| **Chemistry** | |
| **Electrolytes** | Bicarbonate, calcium, chloride, phosphate, potassium, sodium |
| **Liver function tests** | Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin |
| **Renal function tests** | Blood urea/blood urea nitrogen, creatinine |
| **Other** | Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid |
| **Urinalysis** | Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells |
| **Other** | Lymphocyte T and B cell subset analyses (see Table 5). Regulatory T cells (revised per Amendment 04)<br>PBMCs (revised per Amendment 02)<br>Ig analyses (IgG, IgA, and IgM).<br>Viral screen (HCVAb [Hepatitis C] and HbsAg [Hepatitis B]).<br>Viral characterization (including HSV1, HSV2 and CMV, etc)<br>Serum pregnancy test (females of child bearing potential only)<br>Tuberculosis Interferon Gamma Release Assays<br>Tests for thyroid function (thyroid stimulating hormone, free triidothyronine and free thyroxine) and vitamin B12<br>Blood sample for storage for subsequent testing of immune status<br>Cerebrospinal fluid sampling |

Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials must also be repeated. (revised per Amendment 02)

CMV = cytomegalovirus, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV = herpes simplex virus, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PT = prothrombin time, PTT = partial thromboplastin time.

The 8 different surface markers (including but not limited to CD3, CD4, CD8, CD45, CD19, CD16, CD56, and CD14) and total lymphocyte counts will be measured in order to provide the lymphocyte subset data as shown in Table 5. In addition, Regulatory T cells will be measured. Current sponsor data supports the literature showing there is an age-related decline in lymphocyte subsets (see Appendix 5). These data have been used to revise the LLNs for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts to the population-adjusted LLNs of 396, 157, and 74 cells/µL, respectively) (revised per Amendments 02 and 04).

**Table 5 Lymphocyte Subtypes Inclusive in BD Trucount™**

| Cell Type | Cell Surface Markers |
|---|---|
| T lymphocytes | CD3 |
| T helper cells | CD3+, CD4 |
| Cytotoxic T cells | CD3+, CD8 |
| Mature B cells | CD3-, CD19 |
| Natural killer cells | CD3-, CD16, CD56 |
| Macrophages | CD14 |

(Table 5 revised per Amendment 04)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the case report form [CRF] Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

#### 9.5.1.5.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [bpm], respiratory rate [per minute], body temperature [in centigrade], and weight [kg]) will be obtained at the visits designated in Table 6 and Table 7 by a validated method. Measurements of sitting BP and heart rate will be obtained. All BP measurements should be performed on the same arm, preferably by the same person.

#### 9.5.1.5.5 Physical Examinations

A complete physical examination will be performed at Screening as described in Section 9.5.1.2.1. At Baseline and during the Randomization Phase, routine physical examinations will take place as shown in Table 7. These examinations will include the cardiovascular system, respiratory system, and neurological system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.6 Electrocardiograms

Electrocardiograms will be obtained as designated in Table 6 and Table 7. Twelve-lead standard ECGs will be recorded in triplicate (1 minute apart) after subjects have been resting

in the supine position for at least 5 minutes.

On any study day when ECG, vital signs, and blood samples are taken, these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.7 SAFETY MRI

Safety brain MRI assessments will be performed at the times shown in Table 6 and Table 7. Additional safety MRI scans can be performed at unscheduled visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Safety MRIs will be acquired using a standardized procedure that will include fluid-attenuated inversion recovery (FLAIR), gradient-echo, T1, and diffusion-weighted sequences to determine the presence of focal lesions including, but not limited to, evidence for ischemic and hemorrhagic stroke, subdural hematoma, neoplasm, arteriovenous malformation, micro and macrohemorrhages, superficial siderosis, lacunar infarcts, white matter abnormalities, and vasogenic edema. The imaging sequence for the Screening/safety MRI will include: T2 weighted anatomic MRI to rule out major white matter changes, cerebral infarction or other structural lesions, and a high-resolution 3D T1-weighted scan with isotropic voxels with volumes of 1 $mm^3$ or less. In addition, both FLAIR for the detection of vasogenic edema and T2 Gradient Recall Echo for the detection of microhemorrhages will be acquired. The 3D dataset will be reconstructed in transverse slices in Digital Imaging and Communications in Medicine format. The results of this MRI assessment will also be used as the Baseline Period MRI, against which changes after drug administration will be compared. Further details of the MRI protocol can be found in the Imaging Acquisition Guideline. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, and 18 and at the final Follow-Up Visit (Visit 20). (revised per Amendment 04) In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

At any time during the treatment period, subjects will be discontinued from study drug if they develop any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. All of these features must be reported as study specific AEs (or AEs of special interest). These subjects will undergo an ED Visit within 7 days after discontinuation and 4 Follow-Up Visits at 2, 4, 8 and 12 weeks after the last dose of treatment. (revised per Amendment 04) Subjects will also undertake an

Unscheduled Visit (with MRI) at approximately 30 days after the visit at which such MRI features were first identified. Additional visits may be arranged if clinically indicated in the opinion of the investigator, and may occur later than 12 weeks after the final dose of study drug.

#### 9.5.1.5.8 DERMATOLOGIC ASSESSMENT

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at the times shown in Table 6 and Table 7. These assessments will specifically include evaluation of any areas of depigmentation or any rash.

In addition, subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregiver or informants will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or infection, and the investigator will be required to review such AEs as soon as possible and consider an unscheduled physical and dermatological evaluation. Detailed characteristics of any skin rashes will be captured in the clinical database. Physical examination may be undertaken where indicated. Treatment-emergent abnormal dermatological findings should be reported as AEs.

#### 9.5.1.5.9 NEUROLOGIC EXAMINATION

Neurological examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations as shown in Table 6 and Table 7. Details of these examinations will be captured in an eCRF. The neurological examinations will monitor for new symptoms and signs which will then alert the investigator to consider new CNS pathology (especially slowly-evolving neurological conditions that may not lead to prominent symptoms). Examples of neurological signs that may indicate new CNS pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. In such a situation, the investigator should consider (but not limited to) demyelination in the differential diagnoses, and should discuss with the sponsor's medical monitor further investigations or treatment, which will be decided case by case. Neurological examinations will also include the assessment of cranial nerve function, especially the olfactory nerve; the Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits to objectively test olfaction. Treatment-emergent abnormal neurological findings should be reported as AEs.

#### 9.5.1.5.10 PREGNANCY TEST

At Screening, females of childbearing potential will have a serum pregnancy test. At Baseline and during the Treatment Period, urine samples will be obtained from females of childbearing potential for pregnancy tests (see Table 7).

#### 9.5.1.5.11 COLUMBIA SUICIDE SEVERITY RATING SCALE

An assessment of suicidal ideation and behavior using the C-SSRS will be performed at the designed time points in Table 6 and Table 7. A "yes" answer to Type 4 or 5 suicidal ideation or a "yes" response to any suicidal behavior queries will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

#### 9.5.1.5.12 BIOMARKER SAMPLES

As noted in Section 9.5.1.4.2, CSF (for subjects who consent to CSF sample collection), blood, and DNA samples will be collected and may be used for exploratory biomarker analyses, as well as tested in the event that a subject develops AEs that warrant further investigation. (revised per Amendment 02)

#### 9.5.1.5.13 OPHTHALMIC EXAMINATIONS

An ophthalmic examination will be conducted at Baseline (unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available). An additional examination will be conducted, if the subject experiences visual disturbances during the course of the study or is medically indicated. The ophthalmic examinations should include fundoscopy to look at the optic disc, macula and the rest of the retina, as well as an assessment of visual acuity and visual fields.

### 9.5.2 Schedule of Procedures/Assessments

#### 9.5.2.1 Schedule of Procedures/Assessments

Table 6 presents the Schedule of Procedures/Assessments for the Prerandomization Phase. Screening assessments will be organized into 4 tiers (see below and Figure 2).

Table 7 presents the Schedule of Procedures/Assessments for the Randomization Phase.

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

| Phase | Prerandomization | |
|---|---|---|
| Period | Screening | Baseline |
| Visit | 1 | 2 |
| **Procedures/Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)** | | |
| Informed consent (subject and caregiver or informant) | X (Tier 1) | |
| Subject informed consent for CSF sample collection (voluntary)[a] | X | X |
| Demographics | X (Tier 1) | |
| Medical history[b] | X (Tier 1) | |
| Prior / concomitant medications[c] | X (Tier 1) | X |
| Vital signs including weight[d] | X (Tier 1) | X |
| Height | X (Tier 1) | |
| Complete physical examination | X (Tier 1) | |
| Routine physical examination | | X |
| CBB and ISLT[e] | X (Tier 1) | X |
| MMSE[e] | X (Tier 1) | X |
| CDR[e] | X (Tier 1) | X |
| FAQ[e] | X (Tier 1) | X |
| ADAS-cog$_{14}$[e] | | X |
| 15-item Geriatric Depression Scale | X (Tier 2) | |
| Modified Hachinski ischemic scale | X (Tier 2) | |
| C-SSRS | X (Tier 2) | X |
| 12-lead ECG[f] | X (Tier 2) | X |
| Blood and urine for clinical laboratory tests[g] | X (Tier 2) | X |
| Blood for lymphocyte subset analyses[h] | X (Tier 2) | X |
| Blood for Ig analyses[i] | X (Tier 2) | X |
| Blood for viral screen[j] | X (Tier 2) | |
| Blood for thyroid function tests[k] | X (Tier 2) | |
| Blood for vitamin B12 test | X (Tier 2) | |
| Test for previous TB exposure | X (Tier 2) | |
| Urine drug screen | X (Tier 2) | |
| Serum pregnancy test (females of childbearing potential only) | X (Tier 2) | |
| Urine pregnancy test (females of childbearing potential only) | | X |
| Safety and Volumetric MRI[l] | X (Tier 3) | |
| Amyloid PET scan[m] | X (Tier 4) | |
| Inclusion and Exclusion criteria | X (All tiers) | X |
| Adverse events | X (All tiers) | X |
| CSF sampling for PK, PD and storage[a] | | X |
| Blood sample for PK assessments[n] | | X |
| Blood sample for PD and exploratory biomarker assessments[o] | | X |
| Blood sample for pharmacogenomics | | X |
| Blood sample for storage for immune status[p] | | X |
| Blood sample for PBMC isolation | | X |
| Blood sample for viral characterization[q] | | X |
| Centralized dermatological assessment via photography[r] | | X |
| Neurological examinations[s] | | X |
| Ophthalmic assessment[t] | | X |

(Table revised per Amendments 02 and 04)

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

AChEI = acetylcholinesterase inhibitor, AD = Alzheimer's disease, ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CDR = Clinical Dementia Rating, CMV = cytomegalovirus, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), Ig = immunoglobulin, INR = International Normalized Ratio, ISLT = International Shopping List Task (immediate and delayed recall), LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetics, PET = positron emission tomography, PT = prothrombin time, PTT = partial thromboplastin time, TB = tuberculosis.

Note: Screening assessments/procedures have been organized into 4 distinct tiers. All assessments and procedures in each tier should be completed (see Figure 2), and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures, as long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. Similarly, all screening assessments and procedures must be completed, and eligibility to continue in the study confirmed, before any baseline assessments and procedures commence. Adverse events and eligibility against inclusion and exclusion criteria must be assessed at each stage within the Screening Visit and at the Baseline Visit. (revised per Amendment 01)

Note: All screening and baseline assessments are to be completed within 50 days, plus an additional window of up to 30 days if required (revised per Amendment 02). The interval between availability of the results of the last screening assessment (PET scan) and the first baseline (Visit 2) assessments should be as short as possible and ideally should not exceed 7 days. Visit 3 (Randomization) (see Table 7) should occur no more than 10 days after completion of the Baseline visit (Visit 2) and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion No.20 into account (revised per Amendment 02). Thus, the total Prerandomization Phase may be up to 60 days, plus an additional window of up to 30 days if required (revised per Amendment 02).

a: Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. For those subjects who do consent to CSF sample collection: CSF will be collected by LP after fasting (preferred), or at least 2 hours after the most recent meal. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 [or later postrandomization timepoint] and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. If the LP and cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. The CSF sample will be used for PK and PD assessments. A CSF sample will also be stored for testing in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). (revised per Amendments 01, 02, and 04)

b: To include: mild cognitive impairment and AD history; history of TB, vaccination history against and infections due to varicella zoster virus (chickenpox and herpes zoster or shingles); infections due to HSV1 (orolabial herpes or cold sores) and 2 (genital herpes). Medical history of infections to include: onset, duration, relapse frequency, severity, and treatments. For any active infection within the last 4 weeks prior to randomization, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)

c: Prior and concomitant medications include AChEIs and memantine, and other medications for cognitive decline.

d: Weight, respiratory rate, body temperature, and sitting blood pressure and heart rate will be obtained.

e: To be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). At the Screening Visit, the recommended order of assessments is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. At the Baseline Visit, the assessments are to be conducted in the following order: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). (revised per Amendment 02) At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

f: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

g: Clinical laboratory tests consist of hematology (including PT, PTT, and INR), clinical chemistry, and urinalysis.

h: Lymphocyte subsets will include but are not limited to the following cell surface marker assessments: CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cells), CD16/CD56 (natural killer cells) and CD14 (macrophages). Regulatory T cells will also be measured. Viability staining may also be employed. Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials, must also be repeated. (revised per Amendments 02 and 04)

i: Igs to be analyzed include IgG, IgA and IgM.

j: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

k: Thyroid function tests include thyroid stimulating hormone, free triidothyronine, and free thyroxine.

l: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images. MRI will be read by an approved central reader. Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session. (revised per Amendment 01)

m: PET scanning will be performed with a locally approved β-amyloid imaging agent, eg, Amyvid if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. The PET image will be centrally read for the purpose of determining eligibility for inclusion into the study. An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02)

n: The PK blood sample should be collected on the same day shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

o: The PD and exploratory biomarker blood sample should be collected shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

p: A blood sample will be collected at Baseline and stored. This sample may be used for exploratory biomarkers associated with study drug or disease, or in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

q: Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

r: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. See Section 9.5.1.5.8 for further details.

s: To be performed by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. Section 9.5.1.5.9 details what is included in the neurological examination. The Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits and serves as part of the neurological examination. (revised per Amendment 04)

t: An ophthalmic examination will be conducted at Visit 2 unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available. The ophthalmic examination should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields.

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| Phase | Randomization | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Period | Treatment | | | | | | | | | | | | | | | | | Follow-Up | | | | |
| Visit[a] | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | ED[b] | W2 | 19[c] | W8 | 20[c] | UNS Visit[d] |
| Day | 1 | 8 | 15 | 22 | 29 | 43 | 57 | 71 | 85 | 113 | 141 | 183 | 274 | 365 | 456 | 547 | | 561 | 575 | 589 | 631 | |
| Week | 1 | 2 | 3 | 4 | 5 | 7 | 9 | 11 | 13 | 17 | 21 | 27 | 40 | 53 | 66 | 79 | | 81 | 83 | 87 | 91 | |
| Weeks elapsed since first dose | 0 | 1 | 2 | 3 | 4 | 6 | 8 | 10 | 12 | 16 | 20 | 26 | 39 | 52 | 65 | 78 | | 80 | 82 | 86 | 90 | |
| Nominal months elapsed since first dose | 0 | | | | 1 | | 2 | | 3 | 4 | 5 | 6 | 9 | 12 | 15 | 18 | | | 19 | | 21 | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | | | |
| Routine physical examination | X | | | | X | | X | | X | | | X | X | X | X | X | X | | X | | X[e] | X |
| Inclusion and Exclusion criteria | X | | | | | | | | | | | | | | | | | | | | | |
| Vital signs[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X[e] | X |
| Respiratory rate | | | | | X | | X | | X | X | X | X | X | X | X | X | X | | X | | X[e] | X |
| Weight | | | | | | | | | X | | | X | X | X | X | X | X | | | | X | X |
| Centralized dermatological assessment via photography[g] | | | | | | | | | X | | | X | X | X | X | X | X | | | | X | X |
| Neurological examination[h] | | | | | | | | | | | | X | | X | | X | X | | X | | X | X |
| Ophthalmic examination[i] | | | | | | | | | | | | | | | | | | | | | | X |
| Concomitant medications[j] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | X |
| 12-lead ECG[k] | | | X | | X | | X | | X | | | X | | X | | X | X | | X | | X[e] | X |
| Clinical biochemistry and urinalysis | | | X | | X | | X | | X | | | X | X | X | X | X | X | | X | | X | X |
| Complete blood count | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[l] |
| Blood samples (lymphocyte subset analyses)[l] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[l] |
| Blood samples (Igs)[m] | | | | | X | | X | | X | | | X | | X | | X | X | | X | X | X | X |
| Blood samples (isolation of PBMCs) | | | X | | | | | | X | | | | | | | | | | | | X | |
| Urine pregnancy test (females of CBP only) | X[n] | | | | | | | | X | | | X | X | X | X | X | X | | X | | | X |
| Blood sample (storage for immune status)[o] | | | | | X | | | | X | | | X | | X | | X | X | | X | | X | X |
| CBB and ISLT[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | |
| MMSE[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | |
| CDR[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | |

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| **Phase** | **Randomization** | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | | | | | **Follow-Up** | | | | |
| **Visit**[a] | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **ED**[b] | **W2** | **19**[c] | **W8** | **20**[c] | **UNS Visit**[d] |
| **Day** | **1** | **8** | **15** | **22** | **29** | **43** | **57** | **71** | **85** | **113** | **141** | **183** | **274** | **365** | **456** | **547** | | **561** | **575** | **589** | **631** | |
| **Week** | **1** | **2** | **3** | **4** | **5** | **7** | **9** | **11** | **13** | **17** | **21** | **27** | **40** | **53** | **66** | **79** | | **81** | **83** | **87** | **91** | |
| **Weeks elapsed since first dose** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **10** | **12** | **16** | **20** | **26** | **39** | **52** | **65** | **78** | | **80** | **82** | **86** | **90** | |
| **Nominal months elapsed since first dose** | **0** | | | | **1** | | **2** | | **3** | **4** | **5** | **6** | **9** | **12** | **15** | **18** | | | **19** | | **21** | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | | | |
| ADAS-cog$_{14}$[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | |
| FAQ[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | |
| C-SSRS | | | | | X | | X | | X | | | X | X | X | X | X | X | | X | | X[e] | X |
| Safety and Volumetric MRI[q] | | | | | | | | | | | | X | | X | | X | X | | | | X | X |
| Amyloid PET[r] | | | | | | | | | | | | | | | | X | X | | | | | |
| Telephone contact[s] | | | X | | X | | | | X | | | X | | X | | X | X | | | | | X |
| Blood samples for PK[t] | | | X | | X | | | | X | | | X | | X | | X | X | | | | | X |
| Blood samples for PD and exploratory biomarkers[u] | | | X | | X | | | | X | | | X | | X | | X | X | | X | | X | |
| CSF sampling for PK and PD[v] | | | | | X | | | | | | | | | | | X | X | | | | | X |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[l] |
| Sleep/dream questionnaire[w] | | | | | | | | | | | | | | | | | | | | | | X |
| Randomization | X | | | | | | | | | | | | | | | | | | | | | |
| Dispense study drug[x] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | | |

**Footnotes for Table 7**

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating scale, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), Ig = immunoglobulin, ISLT = International Shopping List Task, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, UNS = unscheduled, W2 = new Week 2 follow-up visit, W8 = new Week 8 follow-up visit. (revised per Amendment 04)

a: Visit 3 should be conducted no more than 10 days after completion of the Baseline visit (Visit 2) assessments and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion #20 into account. (revised per Amendment 02) A window of ±3 days will be permitted for Visit 4 to 14 inclusive. A window of ±10 days will be permitted for Visit 15 to 18 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since first dose" at subsequent visits.

b: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug (Visit W2, 19, W8, and Visit 20, respectively). (revised per Amendments 04 and 05)

c: All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 4 post-treatment Follow-Up visits; 2, 4, 8, and 12 weeks after the last dose of study drug (Visits W2, 19, W8, and 20, respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the post-treatment Follow-Up period. (revised per Amendment 04)

d: Unscheduled visits may be conducted at any time that safety or safety MRI data indicate per protocol or as clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

e: Only if clinically significant abnormalities are found at Visit 19 and the investigator considers it necessary to repeat at Visit 20. Clinical biochemistry, urinalysis, CBC, lymphocyte subsets and Igs should always be performed at Visit 20, regardless of clinical significance at the previous Follow-Up visit. (revised per Amendments 02 and 04)

f: Measurements of body temperature and sitting blood pressure and heart rate will be obtained.

g: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. Additional UNS dermatological assessments should be conducted in response to any dermatological AEs of concern (eg, depigmentation, rash, herpetic lesion).

h: Examples of neurological signs that may indicate new central nervous system pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. The Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits and serves as part of the neurologic examination. (revised per Amendment 04)

i: If the subject experiences visual disturbances during the course of the study, the subject will be referred to a specialist for a further ophthalmic examination, which should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields

j: Please refer to Section 9.4.7, which details prohibited and permitted medications in the study and associated timeframes.

k: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

l: Lymphocyte subsets will include but are not limited to the following cell surface marker assessments: CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [NK cells] and CD14 [macrophages]) and total lymphocytes. Regulatory T cells will also be measured. Viability staining may also be employed. Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a Complete Blood Count, with differentials, must also be performed along with assessment of AEs. (revised per Amendments 02 and 04)

**Footnotes for Table 7**

m: Igs to be analyzed include IgG, IgA, and IgM.

n: An additional assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

o: Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops a TEAE that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

p: These assessments are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The order of assessments will be: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). At visits where the CDR or FAQ are conducted, the investigator will determine whether the informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

q: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images in MRI will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, 18, and 20. In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A volumetric MRI sequence will be collected in all subjects immediately following all safety MRI assessments. (revised per Amendment 01)

r: PET scanning will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks. A PET scan will only be performed at Visit 18 or ED if the subject has a valid Screening PET scan for the purposes of longitudinal analyses; subjects who were determined to be eligible for the study on the basis of an historical PET scan will not have a PET scan performed at Visit 18 or ED (revised per Amendment 02)

s: Site staff will contact the subject or the caregiver or informant the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the caregiver or informant, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

t: Two plasma PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visit 5, Visit 11, Visit 14, and Visit 16 and 4 to 8 hours postdose at Visit 7 and Visit 18 (or ED). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or ED) the PK blood sample should be collected shortly before or shortly after completing the LP. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected, followed by LP at approximately the same time as at previous visits. A second PK blood sample will be collected as close as possible to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

u: PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day. At Visits 5, 11, 14, and 16 the PD blood samples should be collected predose.

v: For subjects who consent to CSF sample collection: Postrandomization CSF sample collection is scheduled at Visit 7 (or later postrandomization timepoint) and Visit 18/ED. If a postrandomization CSF sample is collected later than Visit 7, time-matched plasma PK samples are also required (see Footnote t). All visits at which CSF samples are scheduled to be taken also include blood PK and PD assessments and so the subject will be dosed at the clinic on these days. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 [or later postrandomization timepoint] and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If the LP and the cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already

**Footnotes for Table 7**

stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. . Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendments 01, 02, and 04)

w: Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

x: The first dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time as determined by the PI or Safety Physician for postdose medical observation. (revised per Amendment 02)

#### 9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 6 and Table 7 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 4 tiers (see Table 6, Section 9.5.2, and Figure 2.

See Section 9.5 for a full description of the procedures and assessments to be performed during this study.

Table 8 presents the number of blood and CSF samples, and the total volume of blood and CSF that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety.

**Table 8 Summary of Blood and CSF Sample Volumes**

| Assessment | Total number of collection time points | Number of time points x volume per collection (mL whole blood or CSF) | | Total volume (mL whole blood or CSF) |
|---|---|---|---|---|
| | | Screening and Baseline Periods | Treatment and Follow-Up Periods | |
| **Blood** | | | | |
| Chemistry | 12 | 2 x 2 mL | 10 x 2 mL | 24 mL |
| Hematology | 20 | 2 x 5 mL | 18 x 5 mL | 100 mL |
| Lymphocyte subset analyses[a] | 20 | 2 x 4 mL | 18 x 4 mL | 80 mL |
| PBMC | 4 | 1 x 16 mL | 3 x 16 mL | 64 mL |
| IgA, IgM, IgG | 10 | 2 x 2 mL | 8 x 2 mL | 20 mL |
| PT, PTT for INR | 2 | 2 x 3 mL | None | 6 mL |
| Thyroid function tests (thyroid stimulating hormone, free triidothyronine and free thyroxine) | 1 | 1 x 3 mL | None | 3 mL |
| Viral screen (Hepatitis B and C) | 1 | 1 x 4 mL | None | 4 mL |
| Viral characterization | 1 | 1 x 4 mL | None | 4 mL |
| Vitamin B12 | 1 | 1 x 2 mL | None | 2 mL |
| Serum pregnancy test | 1 | 1 x 2 mL | None | 2 mL |
| Tuberculosis (interferon-gamma release assays) | 1 | 1 x 3 mL | None | 3 mL |
| Sample for immune status | 8 | 1 x 4 mL | 7 x 4 mL | 32 mL |
| PD sample | 9 | 1 x 4 mL | 8 x 4 mL | 36 mL |
| PK analysis | 7 | 1 x 3 mL | 6 x 6 mL | 39 mL |
| Pharmacogenetic sample | 1 | 1 x 3 mL | None | 3 mL |
| All blood samples, total volume whole blood collected | | 80 mL | 342 mL | 422 mL |
| **CSF (For subjects who consent to CSF sample collection) (revised per Amendment 02)** | | | | |
| PD and PK samples | 3 | 1 x 12 mL | 2 x 12 mL | 36 mL |

CSF = cerebrospinal fluid, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetic, PT = prothrombin time, PTT = partial thromboplastin time.

a: Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials must also be performed. Therefore, for each unscheduled or repeat test, an additional 9 mL will be collected (5 mL for hematology and 4 mL for lymphocyte subset analyses)

(Table 8 revised per Amendment 04)

### 9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include vital signs, clinical laboratory assessments, physical examinations, ECG measurements, and reports of AEs. MRI will be used to detect vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage and is a standard evaluation to ensure subject safety. The C-SSRS has been endorsed by the FDA as a measure of potential suicidality (Guidance for Industry Suicidality).

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, in addition to mitigating clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. Details are provided in Section 9.2.5.

### 9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

#### 9.5.4.1 Reporting of Serious Adverse Events

**All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.**

SAEs, regardless of causality assessment, must be collected up to 3 months after the last dose of study drug, ie, through to the final follow-up visit (Visit 20). (revised per Amendment 04) (revised per Amendments 04 and 05) However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

**For urgent safety issues**, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

#### 9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must discontinue study treatment.

#### 9.5.4.3 Reporting of Events Associated with Special Situations

##### 9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

| | |
|---|---|
| Overdose | Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose |
| Misuse | Intentional and inappropriate use of study drug not in accordance with the protocol |
| Abuse | Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects |
| Medication error | Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject |

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

##### 9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2) should always be considered serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

#### 9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

#### 9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

#### 9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

### 9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue study drug or withdraw from the study at any time for any reason. All subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug (Visits W2, 19, W8, and Visit 20, respectively) (see Section 9.1.2.3). (revised per Amendment 04) See Table 7 for full details of the assessments to be performed at these visits. revised per Amendment 05) Subjects who discontinue study drug early (as opposed to subjects whose dosing with study drug is temporarily suspended under Medical Monitor guidance) will not be permitted to restart study drug.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and will provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who withdraw prematurely from the study will be withdrawn for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for withdrawal from the study. Study disposition information will be collected on the Subject Disposition eCRF.

A subject removed from the study for any reason may not be replaced.

### 9.5.6 Abuse or Diversion of Study Drug

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF. (revised per Amendment 04)

### 9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

## 9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

### 9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

### 9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy assessments performed in this study.

## 9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance. (revised per Amendment 05)

### 9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the statistical analysis plan, which will be finalized before the first interim efficacy analysis.

#### 9.7.1.1 Study Endpoints

##### 9.7.1.1.1 PRIMARY ENDPOINT

- Safety and tolerability, which include incidence of TEAEs and SAEs, laboratory parameters, vital signs, and ECG parameters (revised per Amendment 05)

##### 9.7.1.1.2 SECONDARY ENDPOINTS

(revised per Amendments 02 and 05)

- % reduction of Aβ(1-x) and Aβ(1-42) in CSF relative to baseline after from 4 weeks and up to 18 months of treatment

- The population PK parameters of E2609 in CSF and plasma, including the effect of intrinsic and extrinsic factors (including NAT2 phenotype)

#### 9.7.1.1.3 EXPLORATORY ENDPOINTS

(revised per Amendments 01, 02, 04, and 05)

Change from baseline in:

- CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) after at least 4 weeks and at 18 months of treatment
- CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up
- Total hippocampal volume at 12 and 18 months of treatment as measured by vMRI
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months of treatment as measured by vMRI
- Amyloid PET standardized uptake value ratio (SUVR) composite at 18 months for brain amyloid levels as measured
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog$_{14}$, CDR, MMSE, ISLT, CBB, and FAQ

### 9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose exploratory efficacy measurement. (revised per Amendment 05)
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

### 9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: The number (percent) of randomized and treated subjects who completed the study and who withdrew from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and withdrew from the study. The primary reasons for discontinuation from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

Completion of Study Treatment: The number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for discontinuation from the study drug are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, inadequate therapeutic response, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

#### 9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, MMSE and FAQ; categorical variables include sex, age group (≤65 years, age >65 years), race, ethnicity, *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal AD or mild to moderate AD). (revised per Amendment 01)

#### 9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014 or higher). (revised per Amendment 04) The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up period will also be recorded.

#### 9.7.1.6 Efficacy and Biomarker Analyses (revised per Amendment 05)

##### 9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

There is no primary efficacy endpoint. (revised per Amendment 05)

##### 9.7.1.6.2 SECONDARY EFFICACY ANALYSES

An mixed-effects model with repeated measures (MMRM) will be used to analyze the following secondary endpoint:

- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) from 4 weeks and up to 18 months. Data from early discontinuations will also be included. (revised per Amendment 05)

##### 9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

(revised per Amendments 01, 02, 04, and 05)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months. Data from early discontinuations will also be included. (revised per Amendment 04)
- Change from baseline in CSF biomarkers of neurodegeneration (eg, t-tau and p-tau) at 18 months of treatment
- Change from baseline in plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during post-treatment follow-up
- Change from baseline in CSF amyloid and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment, and during post-treatment follow-up
- Change from baseline in total hippocampal atrophy at 12 and 18 months as measured by vMRI
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and 18 months as measured by vMRI
- Change from baseline in Amyloid PET SUVR composite at 18 months for brain amyloid levels

The following efficacy endpoints will be summarized using descriptive statistics:

- Change from baseline in the clinical assessments: ADAS-cog$_{14}$, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months

The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

#### 9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

##### 9.7.1.7.1 PHARMACOKINETIC ANALYSES

The PK Analysis Set will be used for E2609 concentration listings and for summaries of E2609 concentrations in plasma and CSF by dose and day. E2609 metabolite PK data may also be listed and summarized. (revised per Amendment 04)

A population PK approach will be used to characterize the plasma PK of E2609. For this approach, plasma PK data from this study will be pooled with relevant data from Phase 1 studies. As appropriate, the effect of covariates on the PK of E2609 will be evaluated. The PK model will be parameterized for oral clearance (CL/F) and apparent volume of distribution (Vz/F) for E2609. Derived exposure parameters such as steady state area under the concentration time curve (AUC) and average concentration ($C_{avg}$) of E2609 and other derived parameters will be calculated from the model using the individual estimates parameterized for oral clearance and dosing history. (revised per Amendment 04)

##### 9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Pharmacodynamic, PGx, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate statistical analysis plan. Please also refer to Appendix 3.

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). The percentage change from baseline in CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months of treatment will be analyzed and presented graphically. (revised per Amendment 05) Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status. (revised per Amendment 04)

Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels, amyloid load on PET, vMRI, and E2609 dose, plasma, and CSF exposure will be initially explored graphically and any emergent relationship will be explored through population PK/PD modeling. The PK/PD relationship between plasma PK parameters with other biomarkers may also be explored using similar methods. (revised per Amendment 04)

The relationship between plasma and CSF exposure to E2609 and the clinical efficacy scales (eg, MMSE, CDR) will be explored graphically. Additionally, the relationship between plasma exposures of E2609 and select lymphocyte parameters will be explored graphically, and any emergent relationship will be explored using population-based modeling methods. (revised per Amendment 04)

Exposure-safety analyses may also be conducted.

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. The genomic DNA samples may also be stored and used as described in Section 9.7.1.7.2. Details of PGx testing may be provided and reported separately.

#### 9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements, and cognitive decline assessment such as CBB will be summarized by treatment group using descriptive statistics. (revised per Amendment 05)

##### 9.7.1.8.1 Extent of Exposure

The extent of exposure to study drug will be summarized as cumulative extent of exposure in 3-month intervals. The cumulative number and percent of subjects will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as continuous variable as well as categorical variable in 3-month intervals and the number and percent of subjects will be presented by treatment group.

##### 9.7.1.8.2 Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities

(MedDRA). Adverse events will be coded to the MedDRA (Version 17.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and preferred term. A subject will be counted only once within an SOC and preferred term, even if the subject experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and preferred term. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

Adverse events will be summarized by the following subgroups: *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal or mild to moderate AD). (revised per Amendment 01)

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

#### 9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

Lymphocyte subsets measured (including but not limited to CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages] and regulatory T cells) will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose.

Serum IgG, IgM, and IgA will be measured and summarized in the same manner as other laboratory parameters.

#### 9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

#### 9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to the end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 msec
- QTc interval >480 msec
- QTc interval >500 msec

Change from baseline in QTc interval:

- QTc interval increases from baseline >30 msec
- QTc interval increases from baseline >60 msec

#### 9.7.1.8.6 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include CBB (Section 9.7.1.6). (revised per Amendment 05)

### 9.7.2 Determination of Sample Size

A total of 15 subjects per dose group is deemed sufficient to derive adequate safety and PK/PD data to aid in the selection of appropriate doses and the design of the Phase 3 studies that may be planned subsequently. (revised per Amendment 05)

### 9.7.3 Interim Analysis

In order to make decisions about the remainder of the study as well as the full E2609 clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. Investigators, other clinical site staff, subjects, caregivers/informants, and study team will remain blinded to study treatment. (revised per Amendments 03 and 05)

An interim safety analysis will also be conducted when all subjects have completed 12 weeks of treatment (or discontinue study drug early). (revised per Amendments 01, 03, 04, and 05)

### 9.7.4 Other Statistical/Analytical Issues

**Stratification** (revised per Amendment 01)

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

### 9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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(revised per Amendment 01)

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# 11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

## 11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

## 11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

## 11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

## 11.4 Recording of Data

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document, except when a section of the eCRF itself is used as the source document. Any correction to entries made on the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each eCRF. The investigator will report the eCRFs to the sponsor and retain a copy of the eCRFs.

## 11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents.

## 11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

## 11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

## 11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

## 11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

## 11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or CTA executed between the institution/investigator and the sponsor/CRO.

## 11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

## 11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

# 12 APPENDICES

## Appendix 1 Sponsor's Grading for Laboratory Values

(revised per Amendment 01)

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **BLOOD/BONE MARROW** | | | | |
| Hemoglobin (conversion from g/dL×0.6206) | **Female** (ULN=15.9 g/dL)<br><11.1 – 10.0 g/dL<br><111 – 100 g/L<br><6.9 – 6.2 mmol/L<br>**Male** (ULN=17.7 g/dL)<br><12.6 – 10.0 g/dL<br><126 – 100 g/L<br><7.8 – 6.2 mmol/L | <10.0 – 8.0 g/dL<br><100 – 80 g/L<br><6.2 – 4.9 mmol/L | <8.0 g/dL<br><80 g/L<br><4.9 mmol/L;<br>transfusion indicated | life-threatening consequences; urgent intervention indicated |
| Leukocytes (total white blood cell) | <3.40 – 3.0×$10^9$/L<br><3.40 $10^3$/uL – 3000/$mm^3$<br>(ULN=10.80 $10^3$/μL) | <3.0 – 2.0×$10^9$/L<br><3000 – 2000/$mm^3$ | <2.0 – 1.0×$10^9$/L<br><2000 – 1000/$mm^3$ | <1.0×$10^9$/L<br><1000/$mm^3$ |
| Lymphocytes | not applicable | <700 – 500/$mm^3$<br><0.7 – 0.5×$10^9$/L | <500 – 200/$mm^3$<br><0.5 – 0.2×$10^9$/L | <200/$mm^3$<br><0.2×$10^9$/L |
| Neutrophils | not applicable | <1.4 – 1.0×$10^9$/L<br><1400 – 1000/$mm^3$ | <1.0 – 0.5×$10^9$/L<br><1000 – 500/$mm^3$ | <0.5×$10^9$/L<br><500/$mm^3$ |
| Platelets | <155 – 75.0×$10^9$/L<br><155 $10^3$/uL – 75,000/$mm^3$<br>(ULN=379 $10^3$/μL) | <75.0 – 50.0×$10^9$/L<br><75,000 – 50,000/$mm^3$ | <50.0 – 25.0×$10^9$/L<br><50,000 – 25,000/$mm^3$ | <25.0×$10^9$/L<br><25,000/$mm^3$ |
| **METABOLIC/LABORATORY** | | | | |
| Albumin, serum- low (hypoalbuminemia) | **2 - 59 years** (ULN=5.5 g/dL)<br><3.5 – 3 g/dL<br><35 – 30 g/L<br>**59 -69 years** (LLN-ULN)<br><3.6 g/dL – 3 g/dL<br>**69 -79 years** (LLN-ULN)<br><3.5 g/dL – 3g/dL<br>**79 -89 years** (LLN-ULN)<br><3.5g/dL – 3g/dL | <3 – 2 g/dL<br><30 – 20 g/L | <2 g/dL<br><20 g/L | life-threatening consequences; urgent intervention indicated |
| Alkaline phosphatase | **Female:**<br>**18 -19 years**<br>>101 – 3.0×101<br>**19 -61 years**<br>ULN=107<br>**61 -71 years**<br>ULN=112<br>**71 -150 years**<br>ULN=108<br>**Male**<br>**18 -19 years**<br>>127 – 3.0×127<br>**19 -61 years**<br>ULN=102<br>**61 -71 years**<br>ULN=103<br>**71 -150 years**<br>ULN=105 | >3.0 – 5.0×ULN<br>See previous column for ULN values | >5.0 – 20.0×ULN<br>See previous column for ULN values | >20.0×ULN<br>See previous column for ULN values |
| Alanine aminotransferase | **Female:**<br>>32 – 3.0×32 | **Female:**<br>>3.0 – 5.0×32 | **Female:**<br>>5.0 – 20.0×32 | **Female:**<br>>20.0×32 |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| | **Male:**<br>>44 – 3.0 x 44 | **Male**<br>>3.0 – 5.0×44 | **Male:**<br>>5.0 – 20.0×44 | **Male:**<br>>20.0×44 |
| Aspartate aminotransferase | >40 – 3.0×40 | >3.0 – 5.0×40 | >5.0 – 20.0×40 | >20.0×40 |
| Bilirubin (hyperbilirubinemia) | >1.2 – 1.5×1.2 | >1.5 – 3.0×1.2 | >3.0 – 10.0×1.2 | >10.0×1.2 |
| Calcium, serum-low (hypocalcemia) (conversion to mmol×0.25) | <8.5 – 8.0 mg/dL<br><2.13 – 2.0 mmol/L | <8.0 – 7.0 mg/dL<br><2.0 – 1.75 mmol/L | <7.0 – 6.0 mg/dL<br><1.75 – 1.5 mmol/L | <6.0 mg/dL<br><1.5 mmol/L |
| Calcium, serum-high (hypercalcemia) | >10.6 – 11.5 mg/dL<br>>2.65 – 2.9 mmol/L | >11.5 – 12.5 mg/dL<br>>2.9 – 3.1 mmol/L | >12.5 – 13.5 mg/dL<br>>3.1 – 3.4 mmol/L | >13.5 mg/dL<br>>3.4 mmol/L |
| Cholesterol, serum-high (hypercholesterolemia) (conversion to mmol/L ×0.02586) | **0 -19 years**<br>>169 – 300 mg/dL<br>>4.37 – 7.75 mmol/L<br>**19 -150 years**<br>>199 – 300 mg/dL<br>>5.15 – 7.75 mmol/L | >300 – 400 mg/dL<br>>7.75 – 10.34 mmol/L | >400 – 500 mg/dL<br>>10.34 – 12.92 mmol/L | >500 mg/dL<br>>12.92 mmol/L |
| Creatinine | **Female**<br>>1.00 mg/dL – 1.5×1.00<br>**Male**<br>>1.27 mg/dL – 1.5×1.27 | **Female**<br>>1.5 – 3.0×1.00<br>**Male**<br>>1.5 mg/dL – 3.0×1.27 | **Female**<br>>3.0 – 6.0×1.00<br>**Male**<br>>3.0 mg/dL – 6.0 ×1.27 | **Female**<br>>6.0×1.00<br>**Male**<br>>6.0×1.27 |
| Gamma glutamyl transpeptidase | **Female**<br>>60 IU/L – 3.0×60<br>**Male**<br>>65 IU/L – 3.0×65 | **Female**<br>>3.0 – 5.0×60<br>**Male**<br>>3.0 – 5.0×65 | **Female**<br>>5.0 – 20.0×60<br>**Male**<br>>5.0 – 20.0×65 | **Female**<br>>20.0×60<br>**Male**<br>>20.0×65 |
| Glucose, serum-high (hyperglycemia) (conversion to mmol/L ×0.0555) | **Fasting glucose value**<br>>99 – 160 mg/dL<br>>5.5 – 8.9 mmol/L | **Fasting glucose value**<br>>160 – 250 mg/dL<br>>8.9 – 13.9 mmol/L | >250 – 500 mg/dL;<br>>13.9 – 27.8 mmol/L;<br>hospitalization indicated | >500 mg/dL;<br>>27.8 mmol/L;<br>life-threatening consequences |
| Glucose, serum-low (hypoglycemia) | <65 – 55 mg/dL<br><3.6 – 3.0 mmol/L | <55 – 40 mg/dL<br><3.0 – 2.2 mmol/L | <40 – 30 mg/dL<br><2.2 – 1.7 mmol/L | <30 mg/dL<br><1.7 mmol/L<br>life-threatening consequences;<br>seizures |
| Phosphate, serum-low (hypophosphatemia) (conversion to mmol/L ×0.323) | not applicable | <2.5 – 2.0 mg/dL<br><0.8 – 0.6 mmol/L | <2.0 – 1.0 mg/dL<br><0.6 – 0.3 mmol/L | <1.0 mg/dL<br><0.3 mmol/L<br>life-threatening consequences |
| Potassium, serum-high (hyperkalemia) | not applicable | >5.5 – 6.0 mmol/L | >6.0 – 7.0 mmol/L<br>hospitalization indicated | >7.0 mmol/L<br>life-threatening consequences |
| Potassium, serum-low (hypokalemia) | <3.5 mEq/L – 3.0 mmol/L | <LLN – 3.0 mmol/L;<br>symptomatic; intervention indicated | <3.0 – 2.5 mmol/L<br>hospitalization indicated | <2.5 mmol/L<br>life-threatening consequences |
| Sodium, serum-high (hypernatremia) | >144 mEq/L – 150 mmol/L | >150 – 155 mmol/L | >155 – 160 mmol/L<br>hospitalization indicated | >160 mmol/L<br>life-threatening consequences |
| Sodium, serum-low (hyponatremia) | <134 mEq/L – 130 mmol/L | Not applicable | <130 – 120 mmol/L | <120 mmol/L<br>life-threatening consequences |
| Triglyceride, serum-high (hypertriglyceridemia) | 150 – 300 mg/dL<br>1.71 – 3.42 mmol/L | >300 – 500 mg/dL<br>>3.42 – 5.7 mmol/L | >500 – 1000 mg/dL<br>>5.7 – 11.4 mmol/L | >1000 mg/dL<br>>11.4 mmol/L<br>life-threatening consequences |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Uric acid, serum-high (hyperuricemia) | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | Not applicable | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | >10 mg/dL<br>>0.59 mmol/L<br>life-threatening consequences |

LLN = lower limit of normal, ULN = upper limit of normal.

# Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1 through Listing 5. Medications permitted with restrictions are listed in Listing 6 through Listing 8. (revised per Amendment 04) **These may not be all-inclusive listings.** Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-202 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 8 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

## Prohibited Prior/Concomitant Medications

### Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Prohibited from 14 days (or 5 half-lives, whichever is longer) before Randomization until after the last treatment visit** | | |
| **Anti-arrhythmic/ abnormal heart rhythm** | | |
| Amiodarone | Cordarone; Pacerone | Incidence in females greater than males, Torsades de Pointes risk regarded as low |
| Disopyramide | Norpace | Incidence in females greater than males |
| Dofetillide | Tikosyn | |
| Ibutilide | Corvert | Incidence in females greater than males |
| Procainamide | Pronestyl; Procan | |
| Quinidine | Cardioquin; Quinaglute | Incidence in females greater than males |
| Sotalol | Betapace | Incidence in females greater than males |
| **Antihistamine/ allergic rhinitis** | | |
| Astemizole | Hismanal | No longer available in United States |
| Terfenadine | Seldane | No longer available in United States |
| **Anti-anginal/ heart pain** | | |
| Bepridil | Vascor | Incidence in females greater than males |
| **Antibiotic/ bacterial infection** | | |
| Clarithromycin | Biaxin | |
| Moxifloxacin | Avelox | |
| Sparfloxadin | Zagam | |
| **Listing 1 continued** | | |
| **Antimalarial/ malaria infection** | | |
| Chloroquine | Aralen | |
| Halofantrine | Halfan | Incidence in females greater than males |
| **Antipsychotic/ anti-emetic/ schizophrenia/ nausea** | | |
| Chloropromazine | Thorazine | |
| **Gastrointestinal stimulant/ heartburn** | | |
| Cisapride | Propulsid | |

## Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Antinausea/ nausea** | | |
| Domperidone | Motillum | Not available in the United States |
| **Sedative; antinausea/ anesthesia adjunct, nausea** | | |
| Droperidol | Inapsine | |
| **Antibiotic; gastrointestinal stimulant/ bacterial infection; increase gastrointestinal motility** | | |
| Erythromycin | Erythrocin; E.E.S. | Incidence in females greater than males |
| **Antipsychotic/ schizophrenia** | | |
| Haloperidol | Haldol | When given intravenously or at higher than recommended doses, risk of sudden death, QT prolongation, and torsades increases |
| Mesoridazine | Serentil | |
| Thioridazine | Mellaril | |
| **Opiate agonist/ pain control, narcotic dependence** | | |
| Levomethadyl | Orlaam | |
| Methadone | Methadose; Dolophine | Incidence in females greater than males |
| **Anti-infective/ pneumocystis pneumonia** | | |
| Pentamidine | Pentam; NebuPent | Incidence in females greater than males |
| **Antipsychotic/ Tourette's tics** | | |
| Pimozide | Orap | Incidence in females greater than males |
| **Antilipemic/ hypercholesterolemia** | | |
| Probucol | Lorelco | No longer available in United States |
| **Anticancer** | | |
| Arsenic trioxide | Trisenox | Used for leukemia |
| Vandetanib | Zactima | Used for thyroid cancer |

Note: This list is not exhaustive.

QTc = Corrected QT interval.

## Listing 2 Prohibited Medications Within 5 Half-lives or 60 days, Whichever is Longer, Before Randomization and Until after the Last Treatment Visit

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Systemic Immunosuppressants[a,b] and Immunomodulatory therapy** | |
| Azathioprine | Azasan, Imur |
| Ciclosporine | Gengraf, Neoral |
| Dexamethasone | Decadron, Dexasone, Diodex, Hexadrol, Maxidex |
| Fingolimod | Gilenya |
| Methotrexate | Trexall |
| Methylprednisolone | Medrol, Meprolone |
| Mycophenolate | CellCept, Myfortic |
| Prednisolone | Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS |

Note: This list is not exhaustive.

a: Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

b: During the treatment period of the study, short term (not more than 14 days) use of steroids up to the equivalent of prednisolone 40 mg OD is permitted after discussion with the Medical Monitor. Dosing with study drug should be suspended from the time steroid treatment is started. Complete blood count and lymphocyte subsets should be determined prior to starting steroid treatment and continue to be monitored weekly. Study drug may be resumed after discussion with the Medical Monitor when the following conditions are met: (1) treatment with steroids has been completed for at least 1 week; (2) total lymphocytes not <LLN; (3) no lymphocyte subsets are below the discontinuation threshold; (4) the investigator considers that the medical condition which required treatment with steroids has improved or resolved. Weekly testing of lymphocyte subset counts and CBC with differentials is required for 4 weeks following resumption of study drug administration. (revised per Amendment 04)

## Listing 3 Prohibited Medications Within 6 Months Before Randomization

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Immunoglobulin therapy** | |
| Adalimumab | Humira |
| Bevacizumab | Avastin |
| Efalizumab | Raptiva |
| Etanercept | Enbrel |
| Immune globulin IV, IVIG, IGIV | Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S |
| Infliximab | Remicade |
| Omalizumab | Xolair |
| Ranibizumab | Lucentis |
| Other monoclonal antibodies not listed here | |

Note: This list is not exhaustive.

### Listing 4 Prohibited Live Vaccines Within 3 Months Before Randomization Until after the Last Treatment Visit (this does not apply to non-live/inactivated vaccines)

| **Bacterial vaccines** | **Viral vaccines** |
|---|---|
| Bacillus Calmette-Guérin vaccine against tuberculosis | Measles vaccination |
| Cholera vaccination (oral) | Rubella vaccination |
| | Oral polio vaccination (Sabin) |
| | Yellow fever vaccination |
| | Varicella (chickenpox) vaccination |
| | Rotavirus vaccination |
| | Japanese encephalitis vaccination |
| | Live attenuated influenza vaccine (FluMist, Fluenz) |
| Typhoid vaccination (oral) | Mumps vaccination |

Note: This list is not exhaustive

## Listing 5 Strong CYP3A4 Inhibitors Prohibited Within 5 Half-Lives or 14 Days (Whichever Is Longer) Before Randomization Until After the Last Treatment Visit

| Generic name | Brand name(s) |
|---|---|
| boceprevir | Victrelis |
| clarithromycin | Clarithromycin, clarithromycin extended release, Prevpac |
| cobicistat | Tybost, Stribild, |
| conivaptan | Vaprisol |
| danoprevir | |
| elvitegravir | Vitekta, Stribild |
| indinavir | Crixivan |
| itraconazole | Sporanoz, Onmel |
| ketoconazole | Xolegel, Nizoral, Ketodan |
| lopinavir | Kaletra |
| nefazodone | Serzone |
| nelfinavir | Viracept |
| posaconazole | Noxafil |
| ritonavir | Norvir, Kaletra |
| saquinavir | Invirase, Fortovase |
| telaprevir | Incivek |
| telithromycin | Ketek |
| tipranavir | Aptivus |
| troleandomycin | Triocetin |
| voriconazole | Vfend, Voriconazole |

Note: This list is not exhaustive

## Permitted Prior/Concomitant Medications

### Listing 6 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Baseline Cognitive Assessments at Visit 2 and Remain on the Same Stable Dose from Baseline to Final Follow-Up Visit

| **Generic name** | **Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™)** |
|---|---|
| **Cognitive Enhancers** | |
| Donepezil | Aricept |
| Galantamine | Reminyl |
| Memantine | Namenda |
| Rivastigmine | Exelon |

Note: This list is not exhaustive.

## Listing 7 Permitted Medications Used on PRN Basis Which are Not to be Used Within 72 Hours before Cognitive Testing

| **Generic name** | **Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™)** |
|---|---|
| **Opiates** | |
| Morphine | Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol |
| **Opiate Agonists** | |
| Codeine | Codeine |
| Fentanyl | Actiq, Duragesic, Fentora, Onsolis, Sublimaze |
| Meperidine | Demerol, Meperitab |
| Oxycodone | Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol |
| Other opioids or opioid agonists which are used on PRN basis | |
| **Benzodiazepines and sedatives** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Amitriptyline | (various) |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Dothiepin | (various) |
| Estazolam | ProSom |
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |
| Lorazepam | Ativan |
| Midazolam | Versed |
| Olanzapine | Zyprexa |
| Promethazine | Phenergan; others |
| Ramelteon | Rozerem |
| Risperidone | Risperdal |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zolpidem | Ambien; others |
| Zopiclone | (various) |
| Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives | |

Note: This list is not exhaustive

## Listing 7 Permitted Medications Used on PRN Basis Which are Not to be Used Within 72 Hours before Cognitive Testing

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|

PRN = Pro re nata

## Listing 8 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| If to be used on a PRN basis see Listing 7. If to be used chronically, subjects must be on a stable dose for ≥4 weeks before Baseline. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks. | |
| **Antidepressants** | |
| Amitriptyline hydrochloride | Elavil |
| Amoxapine | Amoxapine |
| Bupropion | Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin |
| Citalopram | Celexa |
| Clomipramine hydrochloride | Anafranil |
| Desipramine hydrochloride | Norpramin |
| Desvenlafaxine | Pristiq |
| Doxepin hydrochloride | Prudoxin, Silenor, Sinequan, Zonalon |
| Duloxetine | Cymbalta |
| Escitalopram | Lexapro |
| Fluoxetine | Prozac, Sarafem, Selfemra |
| Fluvoxamine | Luvox |
| Imipramine hydrochloride | Tofranil |
| Isocarboxazid | Marplan |
| Maprotiline hydrochloride | Ludiomil |
| Mirtazapine | Remeron Soltab |
| Nortriptyline hydrochloride | Aventyl, Pamelor |
| Paroxetine | Paxil, Pexeva |
| Phenelzine | Nardil |
| Protriptyline hydrochloride | Vivactil |
| Rasagiline | Azilect |
| Selegiline | EMSAM |
| Sertraline | Sertaraline, Zoloft |
| Tranylcypromine | Parnate |
| Trazodone hydrochloride | Desyrel, Oleptro |
| Trimipramine maleate | Surmontil |
| Venlafaxine hydrochloride | Effexor |

## Listing 8 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Mood Stabilizers (Listing 8 continued)** | |
| Carbamazepine | Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR |
| Lamotrigine | Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR |
| Valproic acid | Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate |
| **Antipsychotics** | |
| Acetophenazine | Tindal |
| Aripiprazole | Abilify |
| Asenapine | Saphris |
| Olanzapine | Zyprexa |
| Chlorpromazine | Thorazine |
| Haloperidol | Haloperidol, Haldol |
| Clozapine | Clozaril, Fazaclo |
| Fluphenazine | Prolixin |
| L-Methylfolate | Deplin, L-Methylfolate Calcium |
| Loxapine | Loxitane |
| Mesoridazine | Serentil |
| Perphenazine | Trilafon |
| Quetiapine | Seroquel |
| Risperidone | Risperdal |
| Thioridazine | Mellaril |
| Thiothixene | Navane |
| Trifluoperazine | Stelazine |
| **Benzodiazepines** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Estazolam | ProSom |

## Listing 8 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |
| Lorazepam | Ativan |
| Midazolam | Versed |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zopiclone | Imovane, Zimovane |
| Zopidem | Ambien, Ambien CR, Intermezzo, Stilnox, Stilnoct, Sublinox, Hypnogen, Zolsana |

Note: This list is not exhaustive.

PRN = Pro re nata

# Appendix 3 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

## Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

## Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In

this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

### Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

### Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed

scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

# Appendix 4 AEs Indicating Signals of Possible Drug Abuse Potential

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| 1 | **Euphoric mood** | Euphoric mood |
| | | Euphoria |
| | | Euphoric |
| | | Exaggerated well-being |
| | | Excitement excessive |
| | | Feeling high |
| | | Felt high |
| | | High |
| | | High feeling |
| | | Laughter |
| 2 | **Elevated mood** | Elevated mood |
| | | Mood elevated |
| | | Elation |
| 3 | **Feeling abnormal** | Feeling abnormal |
| | | Cotton wool in head |
| | | Feeling dazed |
| | | Feeling floating |
| | | Feeling strange |
| | | Feeling weightless |
| | | Felt like a zombie |
| | | Floating feeling |
| | | Foggy feeling in head |
| | | Funny episode |
| | | Fuzzy |
| | | Fuzzy head |
| | | Muzzy head |
| | | Spaced out |
| | | Unstable feeling |
| | | Weird feeling |
| | | Spacey |
| 4 | **Feeling drunk** | Feeling drunk |
| | | Drunkenness feeling of |
| | | Drunk-like effect |
| | | Intoxicated |
| | | Stoned |
| | | Drugged |
| 5 | **Feeling of relaxation** | Feeling of relaxation |
| | | Feeling relaxed |
| | | Relaxation |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Relaxed |
| | | Increased well-being |
| | | Excessive happiness |
| **6** | **Thinking abnormal** | Thinking abnormal |
| | | Abnormal thinking |
| | | Thinking irrational |
| | | Thinking disturbance |
| | | Thought blocking |
| | | Wandering thoughts |
| **7** | **Hallucination** | Hallucination |
| | | Illusions |
| | | Flashbacks |
| | | Floating |
| | | Rush |
| | | Feeling addicted |
| **8** | **Inappropriate affect** | Elation inappropriate |
| | | Exhilaration inappropriate |
| | | Feeling happy inappropriately |
| | | Inappropriate affect |
| | | Inappropriate elation |
| | | Inappropriate laughter |
| | | Inappropriate mood elevation |
| **9** | **Mood disorders and disturbances** | Mental disturbance |
| | | Depersonalisation |
| | | Psychomotor stimulation |
| | | Mood disorders |
| | | Emotional and mood disturbances |
| | | Delirium |
| | | Delirious |
| | | Mood altered |
| | | Mood alterations |
| | | Mood instability |
| | | Mood swings |
| | | Emotional lability |
| | | Emotional disorder |
| | | Emotional distress |
| | | Personality disorder |
| | | Impatience |
| | | Abnormal behavior |
| | | Delusional disorder |
| | | Irritability |
| **10** | **Drug tolerance** | Drug tolerance |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Habituation |
| | | Drug withdrawal syndrome |
| | | Substance-related disorders |
| **11** | **Psychosis** | Psychosis |
| | | Psychotic episode or disorder |
| **12** | **Dissociative State** | Dissociation |
| | | Disconnected |
| | | Derealisation |
| | | Depersonalisation |
| | | Detached |
| | | Sensation of distance from one's environment |
| | | Loss of a sense of personal identity |

# Appendix 5 Eisai Lymphocyte Subset Criteria for Study E2609-G000-202: Justification for a Population-Adjusted Approach

**Introduction:**

The Eisai clinical study, E2609-G000-202, requires the analysis of absolute numbers of various functional subsets of circulating lymphocytes. These are distinguished by identification of various complementary differentiation (CD) markers on the cell surface using fluorescent-labeled antibody reagents and flow cytometry. Current enumeration of certain lymphocyte subsets form part of the immunologically based eligibility criteria for study enrollment, as well as being monitored for safety for enrolled and treatment randomized subjects. The Trucount™ M (Becton, Dickinson and Company [BD], BD Biosciences, San Jose, CA) antibody reagents used for the lymphocyte subset eligibility criteria, provides readouts for both absolute (BD Trucount tubes) and percentage of lymphocyte subsets, and includes the following CD markers: CD3 (T cells), CD4 (T helper cells), CD8 (cytotoxic T cells), CD16/56 (natural killer cells), CD14 (macrophages), and CD19 (B cells).

Trucount lymphocyte subset reference ranges provided by the reagent manufacturer (BD) for both absolute and percentages were established for clinical use as an in vitro diagnostic using standardized reference interval methodology. These LLN for the various lymphocyte subsets are currently being used by the central laboratory for Eisai Study E2609-G000-202 to determine eligibility of screened subjects and as part of safety assessments during post-randomization visits. The eligibility criterion excludes subjects with absolute counts of T and B cell markers (CD4, CD8, and CD19 respectively) less than the reference range lower limit of normal (<LLN) at Screening or Baseline.

**Need to assign age appropriate reference ranges:**

Reference ranges established by the vendor according to working group guidance[3] may not be representative of different subgroup analyses (eg, ancestry, disease state, age, gender, etc.), and therefore interval adjustment may be required depending on the subpopulation of interest. The working group guidance for reference intervals (CLSI, 2010[4]) recommends examining data to determine if >10% of subjects are outliers (ie, more than 10% < LLN), and if so, to initiate development of subgroup-appropriate intervals by analyzing data from the literature or internal studies representing the reference population [a minimum of 120 observations recommended by the guidance.[3]]

Data from the ongoing Study E2609-G000-202 has been examined and greater than 10% of the study population screening samples fall below the manufacturer recommended LLN for the key lymphocyte subsets. The population for Study E2609-G000-202 are patients aged 50 to 85 years old inclusive with Mild Cognitive Impairment due to AD or with Mild to Moderate dementia due to AD. Lymphocyte subset data from a data cut of 93 screened

subjects was analyzed and showed that both CD8 and CD4 had greater than 10% of the subjects with results <LLN (26.9%, <220 cells/mm$^3$ and 13%, <404 cells/mm$^3$, respectively); CD19 had approximately 10% of the subjects with results <LLN (9.7%, <80 cells/mm$^3$).

To further determine if the outlier data observations from the ongoing Study E2609-G000-202 were associated with disease status or age, lymphocyte subset data from additional Eisai studies that included healthy elderly subjects or patients diagnosed with MCI or mild/moderate AD were examined. The individuals from all 3 studies included the same 50-to 85-year-old age range as the current E2609-G000-202 study. The studies evaluated include: (1) Study E2609-A001-002 treatment study (n=50 healthy elderly); (2) Lymphocyte subset pilot study in healthy elderly [n=30]; and (3) Lymphocyte subset pilot study in AD/MCI [n=31]. Screening or baseline sample from all 4 studies had >10% of the CD8 absolute counts below reference LLN, 2 out of 4 had >10% of the CD19 absolute counts below reference LLN and 1 out of 4 had >10% of the CD4 absolute counts out of reference LLN [Table 10, Table 11, and Table 12]. The data suggests that the reference values of LLN for CD4, CD8, and CD19 subsets are not a disease-associated observation but are related to the age of the study population being evaluated.

In addition to the Eisai study data, age related decline in lymphocyte subsets has been described in the literature Yan et.al.[1][2] Analysis was performed using flow cytometry on peripheral blood leukocytes using healthy subjects across the 3rd and 10th decades of life. The results from the Yan study (n=80; 37 males, 43 females) demonstrated that with advancing age there was a significant decline in the percentage of lymphocytes, specifically naive T cells [CD3 *P*=0.03], cytotoxic T cells [CD8 *P*=0.08] and activated B cells [CD20/CD69 *P*=0.03] with certain subsets demonstrating even greater decline in males.[1] The age associated changes in immune capabilities, termed “immunosenescence”, which include degenerative changes in the lymph nodes, effects on lymphocyte subsets and changes in adaptive immunity may underlie the increased risk of infection and cancer and decreased immune function in the elderly. This, along with the data from the four Eisai studies described earlier, support the readjustment of the LLNs for the CD reference ranges used for eligibility in Study E2609-G000-202 such that they are better suited to the older patient population enrolling in this study which is thought to be representative of the wider patient population.

**Determining the new LLN criteria:**

The recommended method for establishing reference intervals is the nonparametric approach where the underlying distribution of the data does not matter. The values received from the data (a minimum of 120 observations representing the subgroup population of interest is recommended) are rank ordered and can be used to evaluate the comparative reference interval.[3]

When data from the 4 Eisai studies are put in rank order (see Table 10, Table 11, and Table 12), and a 10% cut value is applied to each of the 3 CD markers of interest the following age-adjusted LLN values are generated:

**Table 9 Summary of CD4, CD8, and CD19 LLNs and Age-Adjusted LLNs**

| Lymphocyte Subset | Current LLN | Age-adjusted LLN |
|---|---|---|
| CD4 absolute count | 404 cells/$mm^3$ | 396 cells/$mm^3$ |
| CD8 absolute count | 220 cells/$mm^3$ | 157 cells/$mm^3$ |
| CD19 absolute count | 80 cells/$mm^3$ | 74 cells/$mm^3$ |

**Table 10 Summary of CD Counts (Parameter: CD19)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 30 | 203 |
| Mean | 213.47 | 198.49 | 159.20 | 172.77 | 192.57 |
| Median | 189.66 | 163.00 | 118.50 | 159.50 | 164.86 |
| 5th percentile | 84.81 | 59.00 | 38.00 | 69.00 | 59.00 |
| 10th percentile | 102.26 | 81.00 | 42.00 | 70.50 | 74.00 |
| 25th percentile | 139.66 | 104.00 | 75.00 | 100.00 | 104.58 |
| 75th percentile | 261.51 | 225.00 | 225.00 | 246.00 | 246.00 |
| 95th percentile | 376.67 | 443.00 | 424.00 | 384.00 | 402.00 |
| Range | 66.19, 593.48 | 17.00, 1066.00 | 37.00, 455.00 | 39.00, 415.00 | 17.00, 1066.00 |

**Table 11 Summary of CD Counts (Parameter: CD8)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 31 | 204 |
| Mean | 362.72 | 352.18 | 324.63 | 427.74 | 362.20 |
| Median | 364.74 | 330.00 | 344.00 | 315.00 | 336.39 |
| 5th percentile | 115.02 | 138.00 | 86.00 | 100.00 | 115.02 |
| 10th percentile | 170.24 | 151.00 | 159.50 | 153.00 | 157.00 |
| 25th percentile | 253.37 | 213.00 | 204.00 | 217.00 | 230.00 |
| 75th percentile | 465.52 | 425.00 | 405.00 | 494.00 | 438.00 |
| 95th percentile | 614.57 | 716.00 | 557.00 | 988.00 | 702.00 |

**Table 11 Summary of CD Counts (Parameter: CD8)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| Range | 98.45, 702.50 | 37.00, 803.00 | 61.00, 702.00 | 54.00, 2255.00 | 37.00, 2255.00 |

**Table 12 Summary of CD Counts (Parameter: CD4)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 31 | 204 |
| Mean | 846.15 | 839.58 | 789.27 | 804.52 | 828.46 |
| Median | 836.94 | 805.00 | 777.50 | 771.00 | 791.50 |
| 5th percentile | 388.44 | 337.00 | 395.00 | 351.00 | 344.00 |
| 10th percentile | 479.55 | 361.00 | 490.00 | 427.00 | 396.00 |
| 25th percentile | 639.54 | 620.00 | 661.00 | 669.00 | 633.77 |
| 75th percentile | 1031.49 | 1078.00 | 924.00 | 1014.00 | 1039.50 |
| 95th percentile | 1315.55 | 1404.00 | 1124.00 | 1327.00 | 1347.00 |
| Range | 274.90, 1643.55 | 197.00, 1481.00 | 248.00, 1720.00 | 143.00, 1336.00 | 143.00, 1720.00 |

References:

1. Yan et al., Immunity and Ageing 2010 v. 7:4; The effect of ageing on human lymphocyte subsets: comparison of males and females.
2. Wikby et al., Biogerontology 2008 vol 9: 299; The immune risk profile is associated with age and gender: findings from three Swedish population studies of individuals 20-100 years of age.
3. Horowitz eJIFCC 2008 vol. 19 (2) Reference intervals: practical aspects).
4. Horowitz et al., CLSI Vol 28 no. 30 Clinical and Laboratory Standards Institute's (CLSI) newly revised document Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition (C28-A3), published in November 2010 EP28-AC3

# PROTOCOL SIGNATURE PAGE

(revised per Amendment 05)

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01 and 05) |
| **Investigational Product Name:** | E2609 |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |

**SIGNATURES**

Authors:

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Date

# INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study To Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendments 01 and 05) |
| **Investigational Product Name:** | E2609 |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

| Investigator | Signature | Date |
|---|---|---|

# REVISION HISTORY

**Revisions to Version 5.0**

**New version/date: Version 6.0 / 29 Jun 2016 (per Amendment 04)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised number of investigational sites (from 40 to 35) | Feasibility | • Synopsis -<br>  ○ Study Design<br>  ○ Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Removed Exclusion Criterion No. 44 for male subjects regarding restrictions on child bearing | No longer a safety concern; E2609 has not shown a deleterious effect on sperm in preclinical reproductive toxicity studies. | • Synopsis:<br>  ○ Exclusion Criteria<br>• Section 9.3.2 |
| Added option for subjects who provided a CSF sample prior to randomization but who declined the CSF sample collection after 4 weeks of dosing to provide a postdose CSF sample at any point in the study (ie, even after 4 weeks of dosing). | Reflects the added value of CSF data for the PK/PD secondary objective of this study. In addition, given that PK steady state is achieved within the 1st 2 weeks of initiation of dosing, data collected post Week 4 visit is still considered to be applicable in assessment of the steady state effect. | • Synopsis -<br>  ○ Pharmacodynamic Assessments<br>• Section 5.3<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.5.1.3.3<br>• Section 9.5.1.4<br>• Table 6<br>• Table 7<br>• Table 8 |
| Revised details of restrictions to anticoagulant therapy and short-term steroid use revised/moved details regarding antiplatelet drugs to the main body of the protocol | To assist in subject recruitment and retention and considering that the strict restrictions were not necessary for subject safety | • Synopsis -<br>  ○ Concomitant Drug/Therapy<br>• Section 9.4.7<br>• Appendix 2 |
| Removed the >33% decrease from baseline for CD4, CD8, and CD19 as a trigger for more frequent testing of flow cytometry and CBCs. Additional safety monitoring for CD4, CD8, CD19, and CBCs will only be based on the population adjusted LLNs for clinically asymptomatic subjects. | Experience to date has indicated significant variability within the normal range, both for increases and decreases. Absolute counts of lymphocyte subsets are more meaningful than percentage decreases for triggering more frequent monitoring. | • Section 9.3.3<br>• Table 1<br>• Table 2 |

**Revisions to Version 5.0**

**New version/date: Version 6.0 / 29 Jun 2016 (per Amendment 04)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Added option to temporarily suspend study drug for subjects who are clinically asymptomatic but who meet CD4, CD8, or CD19 discontinuation thresholds on 2 consecutive tests. Introduce rules for ability to re-start study drug (ie, rechallenge) in these subjects. Only 1 cycle of temporary suspension and rechallenge with study drug permitted for any individual subject. | To assist in subject retention and to gain knowledge on the behavior of lymphocyte subsets on rechallenge. | • Section 9.3.3<br>• Table 1<br>• Table 2 |
| Added extra blood draw times with focus on lymphocyte subsets, CBCs, and immunoglobulins during the 12-week safety follow-up for all subjects. | To increase frequency of key safety monitoring parameters in post-treatment follow-up period so as to assess immunological changes after completion of study drug | • Synopsis<br>  ○ Study Design<br>  ○ Safety Assessments<br>• Section 9.1.2.2<br>• Section 9.1.2.3<br>• Section 9.2.6<br>• Section 9.3.3<br>• Table 7<br>• Table 8<br>• Section 9.5.1.5.7<br>• Section 9.5.5 |
| Clarified that the Functional Assessment Questionnaire is to be administered to the informant/caregiver, and not the subject. | Clarification | • Synopsis<br>  ○ Efficacy Assessments<br>• Section 9.5.1.3.1 |
| Added clarification that the Brief Smell Brief Small Identification Test will be administered as part of the neurological examination | Clarification | • Synopsis<br>  ○ Safety Assessments<br>  ○ Interim Analyses<br>• Section 9.1.1.2<br>• Section 9.5.1.2.1<br>• Section 9.5.1.5.9<br>• Table 6<br>• Table 7 |

**Revisions to Version 5.0**

**New version/date: Version 6.0 / 29 Jun 2016 (per Amendment 04)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised number of randomized subjects in Stage A to n=60±20% | To allow for additional randomization based upon current number of subjects in screening at the time of amendment implementation | • Synopsis<br>  ○ Study Design<br>  ○ No. of Subjects<br>• Section 7<br>• Section 9.1<br>• Section 9.2.1<br>• Section 9.2.6<br>• Section 9.3<br>• Section 9.7.3 |
| Grammatical, typographical, and formatting corrections | Consistency | various |

**Revisions to Version 4.0**

**New version/date: Version 5.0, 06 Feb 2016 (per Amendment 03)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Add interim analyses of safety, and PK/PD data throughout Stage A | Decision making regarding the remainder of the study and the full E2609 clinical development program | • Synopsis –<br>o Exploratory Endpoint Analysis<br>o Interim Analysis<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.4.6<br>• Section 9.7.1.7.1 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Grammatical, typographical, and formatting changes | | Throughout |
| Mandatory nature of CSF collection in study changed to voluntary. This change impacts the timing and details of the PK/PD interim analyses. It also impacts the nature of the CSF-related objectives, which will now be identified as exploratory. | To increase rate of subject consent into the study | • Synopsis –<br>o Secondary Objectives<br>o Exploratory Objectives<br>o Study Design<br>o Exclusion Criterion No. 12<br>o Pharmacokinetic Assessments<br>o Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments<br>o Safety Assessments<br>o Secondary Endpoints<br>o Exploratory Endpoints<br>o Analysis for the Secondary Endpoints<br>o Analysis for the Exploratory Endpoints<br>• Section 5.3<br>• Section 8.2<br>• Section 8.3<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.2.6<br>• Section 9.3.2<br>• Section 9.4.6<br>• Section 9.5.1.3.3<br>• Section 9.5.1.4<br>• Section 9.5.1.5.12<br>• Section 9.7.1.1.2<br>• Section 9.7.1.1.3<br>• Section 9.7.1.6.2<br>• Section 9.7.1.6.3<br>• Appendix 2, Listing 2 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Extended the range of cognitive impairment in delayed recall that would be considered inclusionary for the study and removed the eligibility nature of the cognitive tests repeated at the Baseline Visit. | Original delayed recall aspect of inclusion criterion #1 was considered to be too restrictive and was unnecessarily screening out subjects with MCI/prodromal AD. The eligibility nature of the cognitive tests repeated at the Baseline Visit has been removed in order to simplify the requirements of the pretreatment period for the study. | • Synopsis –<br>  ○ Inclusion/ Exclusion Criteria<br>• Section 9.3.1<br>• Section 9.3.2 |
| Addition of historical amyloid PET scans for determination of eligibility for the study. Subjects with historical PET scans will not be part of the longitudinal PET analyses and therefore will not require a second PET scan at either Visit 18 or ED. | To provide the sites with greater operational flexibility and reduce subject burden. | • Synopsis –<br>  ○ Inclusion/Exclusion<br>  ○ Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments<br>• Section 9.1.1<br>• Section 9.2.5.3<br>• Section 9.3.1<br>• Section 9.5.2<br>• Table 6<br>• Table 7 |
| Added the need for safety laboratory tests to be repeated for subjects whose pre-treatment period is extended due to active infection. | To ensure that all baseline safety laboratory tests are repeated for subjects whose pretreatment period is extended. | • Synopsis –<br>  ○ Inclusion/Exclusion<br>• Section 9.3.2<br>• Section 9.5.2<br>• Table 6 |
| Clarified that exclusion criterion No. 22 (exclusion of subjects with CD4, CD8, or CD19 absolute counts below the LLN) applies to flow cytometry tests conducted at both the Screening and the Baseline Visits. Furthermore, LLNs that are adjusted for the subject population under study will be used. | It was not clear that Exclusion Criterion No. 22 applied to both the Screening and the Baseline Visits. The LLNs for CD4, CD8 and CD19 absolute counts require adjustment for the age of the patient population in this study. | • Synopsis –<br>  ○ Inclusion/ Exclusion Criteria<br>• Section 9.3.2 |
| Provided additional detail | Added to provide clarity | • Synopsis – |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| regarding scope of Exclusion Criterion No. 34 which excludes subjects with hypopigmentation conditions. | for the sites. | ○ Exclusion Criteria<br>• Section 9.3.2 |
| Revised number of clinical sites from 30 to 40 | For feasibility purposes | • Synopsis –<br>○ Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Relaxed the requirement for the cognitive assessments at Screening Visit 1 to be conducted in a certain order and revised the recommended order in which the assessments could be conducted. | To provide the sites with greater operational flexibility. | • Section 9.1.1<br>• Figure 2<br>• Section 9.5.1.3.1<br>• Section 9.5.2<br>• Table 6 |
| Clarify the duration for which the Safety magnetic resonance imaging (MRI) scan, the amyloid PET scan and the lumbar puncture (LP) collected CSF conducted at Screening are considered valid. | To provide sites with greater operational flexibility, particularly for re-screening of screen fail subjects. | • Section 9.1.1 |
| Clarify that for subjects meeting criteria for weekly monitoring of lymphocyte subsets, these can be accommodated within the scheduled clinic visits during the early stages of the treatment period of the study. | To provide operational clarity to the sites. | • Synopsis –<br>○ Exclusion Criteria<br>• Section 9.3.2<br>• Section 9.3.3<br>• Section 9.5.1.5.3 |
| Added the requirement for complete blood counts (CBC) with differentials to be performed whenever repeat or unscheduled flow cytometry tests are performed. | Such that CBC data are available at all times when flow cytometry data is available. | • Section 9.3.3<br>• Table 1<br>• Section 9.5.2<br>• Table 6<br>• Table 7 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015 (per Amendment 02)**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Added 30 day window to the duration of the pre-treatment period if required for medical or operational reasons. | To provide the sites with greater operational flexibility. | • Synopsis –<br>  ○ Study Design<br>  ○ Duration of Treatment<br>• Section 9.1<br>• Figure 1<br>• Section 9.1.1<br>• Section 9.1.1.2<br>• Section 9.5.2<br>• Table 6 |
| Clarified the timing of the start of the Randomization Phase | Clarification | • Section 9.1.1<br>• Section 9.1.2<br>• Section 9.5.2<br>• Table 6<br>• Table 7 |
| Increased number of MCI/Prodromal or mild to moderate AD subjects screened for entry into the study | To reflect the higher screen failure rate than originally anticipated | • Synopsis –<br>  ○ Number of Subjects |
| Removal of CD127 cell surface markers | FoxP3 is the most accepted marker to measure T regulatory cells and additional assessment of CD127 is not required. | • Section 9.5.1.5.3<br>• Table 4<br>• Section 9.5.2.1 |
| Made the clinical biochemistry, urinalysis, CBC, lymphocyte subsets, and immunoglobulin tests mandatory at Visit 20, regardless of clinical significance at Visit 19. | For more comprehensive safety data at the second follow-up visit. | • Section 9.5.2<br>• Table 7 |
| Corrected reference to Exclusion Criterion No. 20 (and not to Exclusion #19) in footnote to Table 6 and Table 7 regarding timing of Visit 3 in relation to Visit 2. | Correction | • Section 9.5.2<br>• Table 6<br>• Table 7 |
| Revised details regarding prohibited antiplatelet drugs | To distinguish between those subjects who consent to CSF sample collection and those who do not | • Appendix 2, Listing 2 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015 (per Amendment 01)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised inclusion to allow for enrollment of mild to moderate AD subjects in Stage A and expand the Stage B mild AD cohort to also include moderate AD subjects | To collect safety data in a wider range of AD patients. | • Title Page<br>• Synopsis –<br>  ○ Objectives<br>  ○ Study Design<br>  ○ Number of Subjects<br>  ○ Inclusion/Exclusion Criteria<br>  ○ Study Treatments<br>  ○ Efficacy Assessments<br>  ○ Study Endpoints<br>  ○ Efficacy Analyses<br>  ○ Interim Analyses<br>  ○ Adaptive Randomization<br>  ○ Sample Size<br>• Section 5.3<br>• Section 7<br>• Section 8 (and all subsections)<br>• Section 9.1<br>• Section 9.1.1<br>• Figure 1<br>• Section 9.2.1<br>• Section 9.2.2<br>• Section 9.2.3<br>• Section 9.2.5.3<br>• Section 9.2.5.4<br>• Section 9.3<br>• Section 9.3.1<br>• Section 9.3.2<br>• Section 9.4.1<br>• Section 9.4.3<br>• Section 9.4.4<br>• Section 9.5.1.3.1<br>• Section 9.7.1.1.2<br>• Section 9.7.1.1.3<br>• Section 9.7.1.4<br>• Section 9.7.1.6<br>• Section 9.7.1.6.2<br>• Section 9.7.1.6.3<br>• Section 9.7.1.8.2<br>• Section 9.7.3<br>• Section 9.7.4 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015 (per Amendment 01)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised inclusion criteria for MMSE to ≥16 from ≥20 | The MMSE score is used as a cut-off for the most impaired subject that would be eligible for the study. Lowering the MMSE inclusion from ≥20 to ≥16 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD cohort. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.1 |
| Revised inclusion criteria for FAQ to ≤24 from ≤20 | As for the MMSE, the FAQ score is used as a cut-off for the most impaired subject that would be eligible for the study. Revising the FAQ inclusion from ≤20 to ≤24 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD cohort, and is consistent with an MMSE inclusion of ≥16. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.1 |
| Revised exclusion criteria such that small arachnoid cysts are not necessarily exclusionary | Arachnoid cysts are a common finding in otherwise healthy subjects. Small lesions (<1 cm in diameter) are generally not considered clinically significant and if discovered incidentally no long term follow up is routinely required. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised exclusion criteria for Ig (IgG, IgA, or IgM) to specify that levels below the LLN at Screening or Baseline need not be exclusionary | For subjects with a Screening or Baseline IG level <LLN to be considered for continuation in the study, assessment of clinical significance of the finding will be required. A finding of "not clinically significant" must be agreed between the Investigator and Medical Monitor in order for the subject to continue in the study. | • Synopsis –<br>○ Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised text to provide instructions for subject assent and associated consent by a legal representative for subjects who the Investigator considers not to have the capacity to consent themselves | With the expansion of the patient population to include moderately demented subjects it was necessary to provide directions regarding the consenting process for subjects considered to be lacking the | • Section 5.3 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015 (per Amendment 01)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | capacity to consent themselves. | |
| Revised number of clinical sites to 30 from 25 | For feasibility purposes. | • Synopsis –<br>  ○ Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Added allowance for Tier 1 and Tier 2 screening assessments to be performed on the same day | Added to provide operational clarity for the sites. | • Section 9.1.1.1<br>• Table 6 |
| Removed requirements for MRIs to include sequences for resting state functional MRI | This was an error and should not have been included in the original protocol. | • Table 6<br>• Table 7 |
| Revised text to clarify that on visits where CSF collection takes place, the CSF collection need not take place on the same day as the cognitive testing for that visit | Added to provide operational clarity for the sites. | • Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised text to clarify that the most important efficacy assessment to keep blinded from safety data is the CDR. | Added to provide operational clarity for the sites. | • Synopsis –<br>  ○ Safety Assessments<br>• Section 9.4.6<br>• Section 9.5.1.5 |
| Revised text to allow PK blood sample and PD blood samples to be taken either shortly before or shortly after the LP on CSF days | Added to provide operational flexibility for the sites. | • Section 9.5.1.4.1<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised Sponsors Grading for Laboratory Values for the following analytes: lymphocytes, neutrophils, albumin, creatinine, phosphate, and potassium serum-high (hyperkalemia) | Corrections made to align with the values for grading used by the central clinical laboratory for this study. | • Appendix 1 |
| Revised details regarding prohibited antiplatelet drugs | Previous version incorrectly referenced a biomarker subgroup. All subjects in this study will need to provide CSF samples. | • Appendix 2; Listing 2 |
| Revised grammar, spelling, etc. | Compliance with current company style guide and for general consistency. | Throughout protocol |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revisions to grammar, spelling, etc. | Compliance with current company style guide and for general consistency | • Throughout protocol |
| Revisions made per new company protocol template | Alignment with current Eisai template | • Synopsis –<br>  ○ Inclusion/Exclusion Criteria<br>• Section 9.1.2.3<br>• Section 9.3.1<br>• Section 9.3.2<br>• Section 9.5 (related subsections)<br>• Section 9.5.4<br>• Section 9.5.4.1<br>• Section 9.5.4.2<br>• Section 9.5.4.3 |
| Clarified classification of MCI due to AD | Clarification that MCI due to AD population will also be consistent with the research criteria for Prodromal AD in that impaired episodic memory is required and will be tested using a list learning task (the International Shopping List Task) | • Synopsis –<br>  ○ Study Design<br>• Section 9.1 |
| Replaced "enroll" with "randomize," pertaining to subject entry into study | Correction to terminology | • Synopsis –<br>  ○ Study Design<br>• Section 9.1<br>• Section 9.3 |
| Added criterion excluding subjects with hepatic impairment and total bilirubin greater than 1.5×ULN or INR greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded. | At request of FDA, exclude subjects who have hepatic impairment | • Synopsis –<br>  ○ Inclusion/Exclusion Criteria<br>• Abbreviation List<br>• Section 9.3.2 |
| Added coagulation parameters for prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR) to screening and baseline procedures | Screen for hepatic impairment | • Synopsis –<br>  ○ Inclusion/Exclusion Criteria<br>• Abbreviation list<br>• Section 9.3.2<br>• Table 4<br>• Table 6<br>• Table 8 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| For subjects who discontinue study drug prematurely, conduct efficacy assessments postdose at same time points as subjects who continue in the study. Added FAQ to this set of efficacy assessments. | To facilitate efficacy analyses, which are based on longitudinal modeling for all subjects | • Synopsis –<br>  ○ Study Design<br>• Section 9.1.2.2<br>• Section 9.3.3<br>• Section 9.5.4.1<br>• Section 9.5.5<br>• Table 7 |
| Delete diagram of E2609 structure | This display is not needed for the protocol. The Investigator's Brochure has this information. | • Section 9.4.2.1 |
| Additional blood samples to be taken at Visits 19 and 20 | Samples are to be put in storage to allow for assessment of immune status at end of study, as needed. | • Synopsis –<br>  ○ Assessments<br>• Table 8 |
| Add subheadings to Section 9.7 describing the primary endpoint analysis, and text clarifying that no multiplicity adjustments will be done to account for the interim analyses | To distinguish clearly the primary analysis and the sensitivity analyses of the primary endpoint | • Synopsis –<br>  ○ Efficacy Analyses<br>• Section 9.7.1.6.1 |
| Clarification of PK sampling upon Early Discontinuation | Additional operational details of the timing of the PK sampling at the ED visit provided | • Section 9.5.1.4.1<br>• Table 7 |
| Clarification of ApoE testing | Clarification that the ApoE genetic testing will be for homozygous or heterozygous E4, versus non-E4 | • Section 9.5.1.4.2 |
| Revision to PK/PD interim analysis text | Confirm that interim PK/PD analysis will be conducted by an independent group | • Section 9.4.6 |
| Addition of text regarding safety signals with E2609 | To provide information on safety-driven dose adjustments | • Synopsis –<br>  ○ Study Design<br>• Section 9.1 |
| Addition of PBMC collection/assessment at Baseline, during treatment, and post-treatment | Recent animal studies have shown an effect of E2609 on this model so they will be added to the 202 clinical study as an additional exploratory assessment. | • Synopsis –<br>  ○ Safety Assessments<br>• Section 9.2.6<br>• Section 9.5.1.5<br>• Table 4<br>• Table 6<br>• Table 7<br>• Table 8 |
| Stipulate that exploratory biomarker analyses may be conducted using blood or CSF samples that may have been drawn for other purposes | To allow more flexibility for possible exploratory biomarker studies associated with study drug or disease, including miRNA and DNA | • Synopsis –<br>  ○ Assessments<br>• Abbreviation list<br>• Section 9.5.1.4.2<br>• Section 9.5.1.5.12<br>• Table 6 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | | • Table 7 |
| Prohibit concomitant medications that are strong CYP3A4, inhibitors, but clarify that no restrictions are needed for other CYP3A4 inhibitors, CYP3A4 inducers, or CES2 inhibitors | At request of FDA, in light of finding that inhibition of CYP3A4 by a reference agent increases plasma levels of E2609 | • Synopsis –<br>○ Concomitant Drug/Therapy<br>• Section 7.1<br>• Section 9.4.7<br>• Appendix 2, Listing 6 |
| Addition of tests for viral characterization at Baseline | To confirm by serology information of subjects prior exposure to common viruses pre-dosing with study drug | • Section 9.5.1.2.2<br>• Table 4<br>• Table 6<br>• Table 8 |
| Use of a centralized dermatologist assessment via photography | A centralized approach, using standardized photography, to FDA-required serial dermatological assessments will be employed for consistency of assessments between sites and for consistency of longitudinal assessments of individual subjects. | • Synopsis –<br>○ Safety Assessments<br>• Section 9.2.6<br>• Section 9.5.1.5<br>• Section 9.5.1.5.8<br>• Table 6<br>• Table 7 |
| Removal of testing for benzodiazepines or opioids as part exclusion criteria #35 | To differentiate appropriate medicinal use from recreational drug use or abuse | • Synopsis –<br>○ Exclusion Criteria<br>• Section 9.3.2 |
| Addition of analysis of other covariates such as adjusted hippocampal volume will be studied | Hippocampal volume has been shown to correlate with rate of cognitive decline and as such is a key covariate to be used in the analyses. | • Synopsis –<br>○ Analysis of Primary Endpoint<br>• Section 9.7.1.6.1 |
| Addition of clarifications to ophthalmic examination | To provide more detail around the requirements for the ophthalmic exam | • Synopsis –<br>○ Safety Assessments<br>• Section 9.5.1.5.13<br>• Table 6<br>• Table 7 |
| Addition of details regarding specific method of CSF collection (ie, gravity drip) | Use of materials required for suction method when collecting CSF can affect the PD data and so it is important to make it clear that only the gravity drip method can be used for collecting CSF in this study for protecting the quality and the consistency of the CSF PD data. | • Section 9.5.1.3.3<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Addition of specific testing for B12 levels at Screening | Abnormally low serum vitamin B12 levels are exclusionary for the study (exclusion criterion 8) but a | • Synopsis –<br>○ Exclusion Criteria<br>• Section 9.3.2 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | blood draw for Vitamin B12 was inadvertently missed out of Table 6 in protocol version 1. | • Section 9.5.1.2.3<br>• Figure 2<br>• Table 6 |
| Addition of details regard AEs that might be signals of possible drug abuse potential | Changed terminology re: collection of additional information for AEs that might be signals of possible abuse potential. No longer use the word "narrative" in order to avoid potential confusion with standard clinical trial narratives eg, for serious adverse events, adverse events leading to withdrawal, etc. | • Synopsis –<br>○ Safety Assessments<br>• Section 9.2.6<br>• Section 9.5.1.5.1<br>• Appendix 4 |
| Addition of clarification regarding position for taking vital signs (ie, supine) | The American Heart Association guidelines only mention supine, standing, and sitting as positions for taking HR and BP measurements. Therefore, have changed required position from semi-supine to sitting. | • Section 9.5.1.5.4<br>• Table 6<br>• Table 7 |
| Stipulated that study drugs are to be taken with food | For consistency of treatment conditions | • Section 9.5.1.4.1 |
| Change to list of Study Specific AEs which should be considered SAEs | Eisai's standard procedures have changed such that non-serious study specific adverse events of interest are no longer reported to Eisai Product Safety; instead, any additional information required for such non-serious adverse events will be obtained through other methods. In addition, certain events (new onset seizures, ocular herpes) are now to be classified as serious as important medical events, regardless of whether they meet standard ICH serious criteria. | • Section 9.5.1.5.1<br>• Section 9.5.1.5.2 |
| Increased blood volume for PK | To match collection tubes and ensure sufficient sample for planned assays | • Table 8 |
| Corrected error in definition of PK analysis set | For accuracy | • Synopsis –<br>○ Study Endpoints<br>• Section 9.7.1.2 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014 (revised original protocol)

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Addition of details regarding discontinuation of study drug | To clearly and consistently differentiate "discontinuation from study drug" from "withdrawal from study" | • Synopsis<br>• Section 7<br>• Section 9.1.2.1<br>• Section 9.2.6<br>• Section 9.3.3<br>• Table 1<br>• Table 2<br>• Section 9.4.1<br>• Section 9.4.4<br>• Section 9.5.1.5.1<br>• Section 9.5.1.5.3<br>• Section 9.5.5 |
| Re-ordered prohibited medication lists | For consistency, all lists re-ordered in alphabetical order of generic drug name, and footnotes revised for overall consistency | • Appendix 2 |
| Moved nefazodone from Listing 9 to Listing 6 | Nefazodone is a strong CYP3A4 inhibitor and is therefore prohibited. | • Appendix 2 |

# 1 TITLE PAGE


## Clinical Study Protocol

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability, and Efficacy of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01) |
| **Sponsor:** | Eisai Inc.<br>155 Tice Boulevard<br>Woodcliff Lake,<br>New Jersey 07677<br>United States<br><br>Eisai Ltd.<br>European Knowledge Centre<br>Mosquito Way<br>Hatfield, Hertfordshire<br>AL10 9SN<br>United Kingdom<br><br>Eisai Co., Ltd.<br>4-6-10 Koishikawa<br>Bunkyo-Ku,<br>Tokyo 112 8088<br>Japan |
| **Investigational Product Name:** | E2609 |
| **Indication:** | Alzheimer's disease |
| **Phase:** | 2 |
| **Approval Date:** | V1.0 15 Jul 2014 (original protocol)<br>V2.0 21 Oct 2014 (revised original protocol)<br>V3.0 28 May 2015 (Amendment 01)<br>V4.0 05 Nov 2015 (Amendment 02)<br>V5.0 06 Feb 2016 (Amendment 03)<br>V6.0 29 Jun 2016 (Amendment 04) |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |
| **GCP Statement:** | This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities. |
| **Confidentiality Statement:** | This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study. |

# 2 CLINICAL PROTOCOL SYNOPSIS

**Compound No.:**

E2609

**Name of Active Ingredient:**

*N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

**Study Protocol Title**

A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability, and Efficacy of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01)

**Investigators**

Stage A: Investigators in United States only

Stage B: Multinational investigators

**Sites**

Stage A: Approximately 35 sites, United States only (revised per Amendments 01, 02, and 04)

Stage B: Approximately 125 sites, globally

**Study Period and Phase of Development**

Stage A: Approximately 32 months and will continue and overlap with Stage B

Stage B: Approximately 42 months from initiation of Stage B (revised per Amendment 01)

Phase 2

**Objectives**

**Primary Objectives**

1. To evaluate the efficacy of daily dosing with 3 doses of E2609 compared with placebo by establishing the lowest effective dose that achieves 90% of the greatest treatment effect (ED90) for E2609 on the derived Alzheimer's Disease Composite Score (ADCOMS) at 18 months of treatment in subjects with Mild Cognitive Impairment due to Alzheimer's Disease/ Prodromal Alzheimer's Disease (referred to as MCI/Prodromal throughout the protocol)
2. To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with Mild to Moderate Dementia due to Alzheimer's Disease (referred to as mild to moderate AD throughout the protocol) (revised per Amendment 01)

**Secondary Objectives** (revised per Amendment 02)

1. To evaluate the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects, as measured by volumetric magnetic resonance imaging (vMRI)
2. To evaluate the efficacy of E2609 compared with placebo on the derived ADCOMS at 18 months in mild to moderate AD subjects (revised per Amendment 01)

**Exploratory Objectives**

(revised per Amendments 01, 02, and 04)

1. To explore the effect of E2609 compared with placebo on the derived ADCOMS following 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
2. To explore the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in mild to moderate AD subjects, as measured by vMRI
3. To explore the effects of E2609 compared with placebo on Aβ(1-x) and Aβ(1-42) in CSF after at least 4 weeks and at 18 months of treatment in MCI/Prodromal subjects and in mild to moderate AD subjects
4. To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during post-treatment follow-up, in MCI/Prodromal and mild to moderate AD subjects, by assessment of:
    a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
    b. The Clinical Dementia Rating (CDR) scale
    c. The Mini-Mental State Examination (MMSE)
    d. The CogState Brief Battery (CBB)
    e. The Functional Assessment Questionnaire (FAQ; also known as the Functional Activities Questionnaire)
    f. The International Shopping List Task (ISLT)
5. To explore the effects of E2609 compared with placebo on various biomarkers in MCI/Prodromal and mild to moderate AD subjects. Biomarkers to be explored may include but are not limited to:
    a. CSF biomarkers of neurodegeneration (eg, total tau [t-tau], phosphorylated-tau [p-tau]) after 18 months of treatment
    b. Plasma and CSF βeta-amyloid converting enzyme 1 (BACE1) measurements during 18 months of treatment and during post-treatment follow-up
    c. vMRI measurements including left and right hippocampal volume, whole brain volume and total ventricular volume at 6, 12, and 18 months of treatment and during post-treatment follow-up
    d. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)
6. To characterize the population pharmacokinetics (PK) of E2609 in MCI/Prodromal and mild to moderate AD subjects, and to examine the effect of intrinsic and extrinsic factors (including N-acetyltransferase 2 [*NAT2*] phenotype) on the PK
7. To explore the relationship between the treatment effects of E2609 on the ADCOMS and its effects on CSF amyloid, CSF BACE1, CSF tau, and vMRI in MCI/Prodromal and mild to moderate AD subjects

**Study Design**

This will be a multicenter, placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild to moderate AD. A common set of inclusion criteria, consistent with the National Institute on Aging–Alzheimer's Association (NIA-AA) clinical research criteria for Mild Cognitive Impairment (MCI) due to Alzheimer's Disease (AD) or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with the criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study will be conducted in 2 stages, Stage A and Stage B. After Stage A subjects have completed 12 weeks of treatment (or have discontinued study drug early), there will be an interim evaluation of the safety and tolerability of chronic dosing with E2609 before expanding enrollment to include a larger number of subjects in Stage B. (revised per Amendments 01 and 04) All MCI/Prodromal subjects will be included in the primary efficacy evaluation irrespective of whether they were recruited during Stage A or Stage B. Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B. All mild to moderate AD subjects will be included in the efficacy evaluations for that cohort. (revised per Amendment 01)

Both Stage A and Stage B will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days, plus an additional window of up to 30 days if required [revised per Amendment 02]) includes a Screening Visit (Visit 1) and a Baseline Visit (Visit 2). All screening assessments (within 4 distinct tiers) must be completed, and eligibility to continue in the study confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

**Stage A**

Stage A will be limited to approximately 35 sites in the United States. (revised per Amendments 01, 02, and 04) Stage A will randomize approximately 60 (±20%) eligible subjects at Visit 3, 1:1:1:1 to 4 treatment groups within each of the 2 clinical populations. (revised per Amendments 01 and 04) In addition to the placebo group, 3 E2609 doses will be used to reduce CSF amyloid β levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/pharmacodynamic (PD) modeling has shown that these doses should achieve these targets when administered once daily (QD) with food, and these doses will be evaluated based on the 4-week assessment of CSF Aβ(1-x) from subjects who provide voluntary consent for CSF measurement. (revised per Amendment 02)

During Stage A, safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the first subject is randomized during Stage A, an independent data safety monitoring board (DSMB; including at least 1 immunologist) will review all safety data in an unblinded manner. The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. Unless the DSMB recommends otherwise, randomization of subjects into Stage A will continue until approximately 60 (±20%) subjects have been randomized and dosed. (revised per Amendments 01 and 04)

Interim analyses of the E2609 plasma PK for all subjects and the E2609 CSF PK and PD profiles will

be performed on baseline data and samples collectedafter at least 4 weeks of study drug. These interim analyses, as well as analyses of safety data, will be performed on an ongoing basis throughout Stage A. Refer to the Interim Analysis section for more detail. These data will be used to evaluate the CSF PD effects of E2609 doses, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels. (revised per Amendments 01 and 02) The mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment for each dose of E2609 and its 90% confidence interval for the median will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data from Stage A and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline after 4 weeks of dosing. (revised per Amendments 01, 02, 03, and 04)

Once Stage A subjects have completed at least 12 weeks of treatment (or discontinued study drug early) an interim safety analysis will be conducted by Eisai and the DSMB. (revised per Amendments 01 and 04) Subjects in Stage A will continue study drug while the DSMB reviews all the available safety data, but randomization of additional subjects will not take place (ie, recruitment into Stage B will not commence) until the safety analysis is completed by the DSMB.

If there are safety signals with one of the E2609 dose groups that would require dose adjustment, changes to dose will be reflected in an amendment to the protocol. Information on how these subjects will be handled in the primary analysis will be described in the Statistical Analysis Plan.

**Stage B**

Stage B will start after the DSMB safety review of Stage A has shown acceptable safety and tolerability of E2609 and after the doses of E2609 to be used in Stage B are evaluated. (revised per Amendment 02) Stage B will enroll, randomize, and dose additional eligible subjects up to a maximum of 500 MCI/Prodromal and up to a maximum of 200 mild to moderate AD. The final total number of MCI/Prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. (revised per Amendment 01) Safety data from Stage B will continue to be reviewed by the DSMB (approximately every 3 months) until recruitment to the study is completed; following this the DSMB will meet approximately every 6 months.

In Stage B, both cohorts will include separate placebo groups. The MCI/Prodromal cohort will include 3 doses of E2609 (5, 15, and 50 mg QD) whereas the Mild to Moderate AD cohort will only include 2 doses of E2609 (15 and 50 mg QD). (revised per Amendment 01)

Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B. Randomization of MCI/Prodromal subjects into Stage B will commence according to a fixed schedule (1:1:1:1; placebo:5 mg E2609:15 mg E2609:50 mg E2609) until a total of 100 MCI/Prodromal subjects (including those from Stage A) have been randomized. (revised per Amendment 01) The remaining subjects in the MCI/Prodromal cohort in Stage B will then be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. The mild to moderate AD subjects will be randomized according to a fixed schedule (1:1:1 placebo; 15 mg E2609; 50 mg E2609) throughout Stage B. (revised per Amendment 01)

**Early Discontinuation**

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug. (revised per Amendment 04) Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie, at Visits 11, 14, 15, 16, 17, and 18) if these visits have not already been performed. At these visits, only the clinical

efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB and ISLT) will be conducted. Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

**Follow-Up**

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 4 post-treatment Follow-Up Visits: 2, 4, 8, and 12 weeks after the last dose of study drug. If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the post-treatment Follow-Up Period. (revised per Amendment 04)

**Number of Subjects**

Stage A: Approximately 400 MCI/Prodromal or mild to moderate AD subjects will be screened to provide approximately 60 (±20%) randomized subjects (a target of approximately 15 subjects per treatment arm). There will be no limit to the number of subjects randomized from either clinical cohort. (revised per Amendments 01, 02, and 04)

Stage B: Up to approximately 2100 MCI/Prodromal subjects will be screened to provide up to 500 randomized subjects. The final number of MCI/Prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. In addition, up to approximately 835 subjects with mild to moderate AD will be screened to provide up to 200 randomized mild to moderate AD subjects. The final number of mild to moderate AD subjects randomized in Stage B will depend upon the number of mild to moderate AD subjects previously randomized during Stage A. (revised per Amendment 01)

**Inclusion Criteria**

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD or AD dementia and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at Screening Visit 1:**
(revised per Amendment 02)

   a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation
   b. Cognitive impairment of at least 1 standard deviation (SD) from age adjusted norms in delayed recall on the ISLT. Alternatively, cognitive impairment of at least 0.5 SD from age-adjusted norms in delayed recall on the ISLT plus impairment of at least 1 SD from age-adjusted norms in at least 1 other computerized learning and memory test (ISLT immediate recall, or 1 of the learning and memory components of the CBB). (revised per Amendment 02)
   c. FAQ ≤24 (revised per Amendment 01)
   d. MMSE ≥16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading; an historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group (revised per Amendment 02)
3. Male or female, age 50 to 85 years, inclusive at time of consent
4. Must have an identified caregiver or informant who is willing and able to provide follow-up

information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.

5. If receiving acetylcholinesterase inhibitors (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.
6. Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization.

**Exclusion Criteria (revised per Amendment 04)**

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or magnetic resonance imaging (MRI)
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and <1 cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could, in the opinion of the investigator, confound the MCI/Prodromal or mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendments 01 and 02)
7. A score of ≥8 on the 15-item Geriatric Depression Scale at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking

vitamin B12 injections, level should be at or above the lower limit of normal (LLN) for the testing laboratory) at Screening

9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
12. Any contraindications to lumbar puncture (LP) for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity). Only applicable to subjects consenting to CSF sample collection (revised per Amendment 02)
13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization
20. Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).

22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below population-adjusted LLN at Screening or Baseline and confirmed by a repeat test conducted 1 week after the initial test. The population-adjusted LLN for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are 396, 157, and 74 cells/μL respectively. (revised per Amendment 02)
23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the Investigator and the Medical Monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of clinical immunodeficiency. The discussion with the Medical Monitor should include a detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)
24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate electrocardiograms (ECGs). A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute at Screening or Baseline
29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.
33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo). Diagnosis of an underlying disease causing hypopigmentation is not necessary for exclusion if the clinical presentation is consistent with such a condition. Hypopigmentation associated with scarring need not be exclusionary. (revised per Amendment 02)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.

36. Has a "yes" answer to the Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the 1st dose of study drug.
43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period and for 28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.
    - Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.

      (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

**Study Treatments**

E2609 tablets of 5-mg, 10-mg, and 25-mg dose strengths will be supplied. Placebo tablets to match E2609 will be of identical appearance. Each subject will receive 2 tablets, which when combined will make up the required doses of E2609 (see below) or placebo, to be administered orally QD with food.

- Stage A: 3 doses (5, 15, and 50 mg) of E2609 or placebo (revised per Amendment 01)
- Stage B, MCI/Prodromal Cohort: 3 doses (5, 15, and 50 mg) of E2609 or placebo (revised per Amendment 01)
- Stage B, Mild to Moderate AD Cohort: 2 doses (15 and 50 mg) of E2609 or placebo (revised per Amendment 01)

**Duration of Treatment**

The maximum duration of a subject's participation in the study will be approximately 2 years, comprising:

- Screening and Baseline Periods (Prerandomization Phase): up to 60 days, plus an additional window of up to 30 days if required (revised per Amendment 02)

  (In subjects who have an active infection within 4 weeks of the planned randomization date, the duration of the pre-randomization phase can be extended by up to 4 weeks to allow additional time for resolution of the infection.)
- Treatment Period (Randomization Phase): up to 78 weeks
- Follow-Up Period (Randomization Phase): 12 weeks (post last dose)

**Concomitant Drug/Therapy**

(revised per Amendment 04)

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit (see Appendix 2 for a detailed listing of these agents):

- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization. However, during the treatment period of the study, short term (not more than 14 days) use of steroids up to the equivalent of prednisolone 40 mg QD is permitted after discussion with the Medical Monitor. Dosing with study drug should be suspended from the time steroid treatment is started. Complete blood count and lymphocyte subsets should be determined prior to starting steroid treatment and continue to be monitored weekly. Study drug may be resumed after discussion with the Medical Monitor when the following conditions are met: (1) treatment with steroids has been completed for at least 1 week; (2) total lymphocytes not <LLN; (3) no lymphocyte subsets are below the discontinuation threshold; (4) the investigator considers that the medical condition which

required treatment with steroids has improved or resolved. Weekly testing of lymphocyte subset counts and CBC with differentials is required for 4 weeks following resumption of study drug administration. (revised per Amendment 04)

Subjects taking AChEIs or memantine must meet the following criteria in order to be included in the primary analyses:

- On a stable dose for 12 weeks before the baseline cognitive assessments at Visit 2
- Remain on a stable dose while on study

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for the primary analyses.

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed. Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before randomization. They may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 04)
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if, in the opinion of the investigator, this will not interfere with study procedures or subject safety, and are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks.

Antiplatelet therapy: (revised per Amendment 04)

- For subjects who consent to CSF sample collection: Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) are permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.
- For subjects who do not consent to CSF sample collection: Aspirin and clopidogrel, individually or in combination, are permitted.

**Assessments**

**Efficacy Assessments**

Derived ADCOMS: The derived ADCOMS represents a new approach to the analysis of selected items (12 total) from 3 fully validated and well established clinical tools, the ADAS-cog (4 items), the MMSE (2 items), and the CDR (all 6 items). The 3 scales should be administered in full in the morning, or, if not possible, consistently at the same time of day.

Alzheimer's Disease Assessment Scale - cognitive subscale: The 14-item version will be used since it is considered more relevant for subjects with MCI/Prodromal AD or mild AD.

Mini-Mental State Examination: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing.

Clinical Dementia Rating: Assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

CogState Brief Battery: A computer-based battery comprising 4 cognitive tests:

- Detection – a simple reaction time test. Speed of response is the measure.
- Identification – a simple choice reaction time test. Speed of response is the measure.
- One Card Back – a simple working memory test. Accuracy of response is the measure.
- One Card Learning – a visual learning and memory test. Accuracy of response is the measure.

International Shopping List Task: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall.

Functional Assessment Questionnaire: The FAQ has 10 items concerned with performing daily tasks necessary for independent living. The caregiver or informant provides performance ratings on 10 complex activities of daily living performed within the preceding 4 weeks. (revised per Amendment 04)

Volumetric Magnetic Resonance Imaging: vMRI will be used to evaluate disease modification, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs.

**Pharmacokinetic Assessments**

Blood samples will be collected for the determination of the concentrations of E2609. For subjects who consent to CSF sample collection, CSF samples will be collected for the determination of E2609 concentrations. (revised per Amendment 02) Analyses of metabolite concentrations may be performed depending on emerging data from other studies with E2609.

**Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments**

Brain atrophy will be measured by vMRI: see Efficacy Assessments (above).

The soluble biomarkers Aβ(1-x), Aβ(1-42), (Aβ(1-40), total tau (t-tau), and p-tau will be measured in subjects who consent to CSF sample collection (revised per Amendment 02). BACE1 levels and activity in CSF will also be measured in subjects who consent to CSF sample collection (revised per Amendment 02). Other exploratory biomarkers and amyloid isoforms (eg, Aβ[1-40]) may also be evaluated in plasma or CSF. (revised per Amendment 04)Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

Amyloid PET imaging will be used to confirm that all subjects eligible for progression to the Baseline Period have amyloid deposition in the brain. An historical amyloid positive PET scan may be used, if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02) Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses) and will only be conducted through to the time at which acceptable 18-month PET scans have been obtained for at least 25 subjects per treatment arm for each

amyloid PET ligand used. (revised per Amendment 02)

Apolipoprotein E (*ApoE*) and *NAT2* genotyping/phenotyping will be conducted. *ApoE4* homozygous or heterozygous status versus non-carriers and *NAT2* status will be used in the statistical analysis to determine the effects on treatment response and safety. Remaining genomic DNA may also be stored for up to 15 years to be used to examine the role of DNA sequence variability on the absorption, distribution, metabolism, and elimination of E2609, development of adverse events (AEs), as well as the underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single-nucleotide polymorphisms with PK, safety, or PD data.

**Safety Assessments**

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR. (revised per Amendment 01) Routine safety assessments will include the monitoring and recording all AEs and serious adverse events (SAEs), monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

Complete blood counts and lymphocyte subset absolute counts and percentages will be measured (by a centralized laboratory) every week for the 1st month, every 2 weeks for the next 2 months (Months 2 and 3) and monthly for the next 3 months (Months 4, 5, and 6). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at all 4 Follow-Up Visits at 2, 4, 8, and 12 weeks after the last dose of study drug. Serum IgG, IgA, and IgM will be monitored monthly for the 1st 3 months, at 6, 12, and 18 months, and at the Follow-Up Visits that occur 4, 8, and 12 weeks after the last dose of study drug. (revised per Amendment 04)

Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and post-treatment for exploratory immunomodulatory and immune-based analyses.

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at baseline and at 3-month intervals during the Treatment Period. These assessments will specifically include evaluation of any areas of depigmentation or rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregivers/ informants will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so such AEs can be reviewed promptly.

Baseline and on-study blood and DNA samples will be taken and stored for all subjects, and CSF samples will be taken and stored for all subjects from whom CSF samples were collected (revised per Amendments 02 and 04). These samples may be tested for exploratory biomarkers associated with study drug or disease, or in the event that a subject develops AEs that warrant further investigation (eg, to test if a subject with a treatment-emergent infection was exposed to any suspected infective agents before treatment with study drug).

Safety brain MRI assessments will be performed at Screening, at 6, 12, and 18 months during the Treatment Period and at the final Follow-Up Visit. Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Full neurologic examinations will be performed at Baseline, at 6, 12, and 18 months, and at the 4- and 12-week Follow-Up Visits, by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. The neurologic examinations will include muscle strength testing and assessment of cranial nerves including olfaction, with the use of the Brief Small Identification Test, as well as other parts of the CNS. (revised per Amendment 04)

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments will include the ADAS-$cog_{14}$, MMSE, and CBB.

An assessment of suicidality using the C-SSRS will be performed at Screening and Baseline and at regular intervals throughout the Treatment and Follow-Up Periods.

An ophthalmic examination (including retinal examination) will be conducted at Baseline. An additional examination will be conducted if the subject experiences visual disturbances during the course of the study.

A number of safety-related criteria for discontinuation of study drug are specified for the study.

**Bioanalytical Methods**

Plasma and CSF concentrations of E2609 will be measured by a validated liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) in both CSF and plasma will be measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendment 04)

BACE1 levels and activity may be measured using a customized assay. Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

**Statistical Methods**

All statistical tests will be based on the 5% (2-sided) level of significance, except for the Bayesian methods on the primary endpoint.

**Study Endpoints**

**Primary Endpoint**

- Change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects

**Secondary Endpoints**

Change from baseline in: (revised per Amendment 02)

- Total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- The derived ADCOMS at 18 months of treatment in mild to moderate AD subjects (revised per Amendment 01)

**Exploratory Endpoints**

(revised per Amendments 01,02, and 04)

Change from baseline in:

- The derived ADCOMS at 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
- Total hippocampal volume at 12 and 18 months of treatment in mild to moderate AD subjects as measured by vMRI
- CSF Aβ(1-x) and Aβ(1-42) after at least 4 weeks and at 18 months of treatment in MCI/Prodromal subjects and in mild to moderate AD subjects
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ in MCI/Prodromal and mild to moderate AD subjects
- CSF biomarkers of neurodegeneration (eg, tau and p-tau) at 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects
- Plasma and CSF amyloid, and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild to moderate AD subjects
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and, 18 months in MCI/Prodromal and mild to moderate AD subjects as measured by vMRI
- Brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- The population PK parameters of E2609 including the effect of intrinsic and extrinsic factors (including *NAT2* phenotype) in MCI/Prodromal and mild to moderate AD subjects

**Analysis Sets**

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set is the subset of subjects in the FAS who sufficiently comply with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 post-treatment PD measurement.

**Efficacy Analyses**

***The MCI/Prodromal cohort:*** This study in the MCI/Prodromal cohort is based on Bayesian adaptive design. Frequent interim analyses will be performed to assess the probability of early success and futility and to make early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis. Key definitions relevant to the Bayesian aspects of the adaptive design are given below.

**Study Definitions**

- **Maximum Effective Dose ($d_{Max}$):** The dose that achieves the greatest treatment effect.
- **$ED_{90}$:** The lowest dose that achieves at least 90% of the $d_{Max}$ treatment effect in the derived ADCOMS.

- **Early Success:** The study in the MCI/Prodromal cohort will meet early success criteria if the probability that the $ED_{90}$ at 18 months of treatment achieves 25% improvement over placebo is at least 80%. Early success is achieved before all MCI/Prodromal subjects complete 18 months of treatment and can only be determined after at least 200 MCI/Prodromal subjects have been randomized. If early success is declared before full randomization, the randomization of new MCI/Prodromal subjects will stop but subjects already randomized into the study will receive the full 18 months of treatment (following confirmation from the Sponsor's Senior Management).
- **Futility:** The study in the MCI/Prodromal cohort will meet statistical futility criteria if the probability that the $ED_{90}$ is better than placebo by the clinically significant difference of 25% is less than 5% at 18 months of treatment. The statistical futility boundary is binding; if the statistical futility boundary is crossed the study will be considered to have failed.
- **Study Success:** The study in the MCI/Prodromal cohort will be considered a success if an $ED_{90}$ at 18 months treatment has at least an 80% probability of achieving 25% improvement over placebo at either an interim analysis or at the final analysis.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)***:*** All mild to moderate AD subjects will be included in the efficacy evaluations of the Mild to Moderate AD cohort. The analysis of the Mild to Moderate AD cohort is based on the group sequential design. Interim analyses in the Mild to Moderate AD cohort will only be performed after the MCI/Prodromal cohort crosses the early success boundary. The early efficacy signal based on the change from baseline of ADCOMS at 18 months is defined as crossing the interim-analysis boundaries for overwhelming efficacy in the mild to moderate AD population. The O'Brien-Fleming (OF) boundaries based on Lan-DeMets alpha spending function will be used to assess overwhelming efficacy. The corresponding OF

boundaries based on *P* values will be 0.076, 0.0221, and 0.0423 for the first, second, and final analyses, respectively, according to 2 planned interim analyses at the 60% and 80% information fraction. (revised per Amendment 01)

**Analysis for the primary endpoint**

***Primary analysis of primary endpoint***

The primary analysis will be based on MCI/Prodromal subjects from the FAS with the prespecified censoring rule applied. The primary endpoint is the change from baseline to 18 months in the derived ADCOMS. The dose-response of the primary endpoint is modelled with a first-order normal dynamic linear model, where Normal and Inverse-Gamma priors are used. The primary efficacy analysis will calculate the Bayesian posterior probability that the dose identified is the most likely $ED_{90}$ dose that achieves 25% improvement over the placebo arm. At each interim analysis and the final analysis, 2 Bayesian probabilities will be summarized for each active dose: the probability it is the $ED_{90}$ dose and the probability of achieving 25% improvement over the placebo arm.

For the clinical efficacy data (ie, derived ADCOMS, MMSE, ADAS-cog, CDR, CBB, ISLT, and FAQ), subjects will be censored at the time of initiation of treatment with AChEIs or memantine, if they were not on these medications at the time of Baseline cognitive assessment (Visit 2), and will be censored at the time of dose adjustment of AChEIs or memantine if they were already on stable treatment with these medications at the time of Baseline cognitive assessment (Visit 2). The value of the primary endpoint for censored subjects will be imputed using data up to the censoring time and Bayesian longitudinal modeling.

***Sensitivity analyses of primary endpoint***

After unblinding, the primary endpoint will be analyzed using the Bayesian methods described above as well as conventional statistical methods. The following additional Bayesian analyses will be conducted as sensitivity analyses:

- The primary endpoint will be analyzed regardless of initiation of treatment, or dose adjustment, with AChEIs or memantine using the same Bayesian analysis method as primary analysis. This is an intent-to-treat analysis without any censoring.
- In case of early success, the primary analysis as well as the above sensitivity analyses will be repeated after all subjects have completed 18 months of treatment or have been lost to follow-up.

Statistical methods for the final conventional analyses will use a mixed-effects model with repeated measures (MMRM) on the change from baseline in the derived ADCOMS at 18 months. The model will include treatment groups, randomization stratification variables (the presence or absence of ongoing treatment with AChEIs or memantine or both, and *ApoE4* status), and baseline ADCOMS as covariates. Other covariates such as adjusted hippocampal volume will be studied. These analyses will be performed as sensitivity analyses on the FAS as well as the per protocol set, and as such, no multiplicity adjustments will be made to account for the interim analyses. In case of early success, the conventional analyses will also be performed using the data collected before the interim analysis.

**Analysis for the secondary endpoints**

***The MCI/Prodromal Cohort***

An MMRM will be used to analyze the following secondary endpoint: (revised per Amendment 02)

- Change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI

Comparisons between each treatment group and placebo will be performed.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

An MMRM will be used to analyze the change from baseline of derived ADCOMS at 18 months in mild to moderate AD. If there is no treatment group-by-population interaction in the overall study, the MMRM analysis will include all subjects (MCI/Prodromal or mild to moderate AD) in the overall study. Otherwise, the MMRM analysis will only include subjects in the Mild to Moderate AD cohort. The comparison between placebo and active doses will be performed within mild to moderate AD subjects regardless of subjects included in the MMRM analysis. Dunnett's method will be used to control for multiplicity due to multiple comparisons.

**Analysis for exploratory endpoints**

(revised per Amendments 01, 02, and 04)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in the derived ADCOMS at 12 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in total hippocampal atrophy at 12 and 18 months in mild to moderate AD subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) after at least 4 weeks and at 18 months in MCI/Prodromal and mild to moderate AD subjects. Data from early discontinuations will also be included.
- Change from baseline in the clinical assessments: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in plasma and CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during post-treatment follow-up in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months as measured by vMRI in MCI/Prodromal and mild to moderate AD subjects

A linear mixed-model will be used to analyze the following exploratory endpoints:

- Change from baseline in brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in CSF biomarkers of neurodegeneration (eg, tau, p-tau) at 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects

Data from early discontinuations will also be used as appropriate. Comparisons between each treatment group and placebo will be performed.

A linear mixed-model with repeated measures will be used to determine the relationship between the following endpoints:

- Change from baseline in the derived ADCOMS score and the change from baseline in biomarkers in CSF at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in the derived ADCOMS score and change from baseline in imaging biomarkers (hippocampal, whole brain, and total ventricular volumes) at 12 and 18 months in MCI/Prodromal and mild to moderate AD subjects

*ApoE* status for heterozygous and homozygous E4 carriers will be included in the model to assess the

effect of *ApoE* status in this relationship.

A population PK approach will be used to characterize the plasma PK of E2609. For this approach, plasma PK data from this study will be pooled with relevant data from Phase 1 studies. As appropriate, the effect of covariates on the PK of E2609 will be evaluated. The PK model will be parameterized for oral clearance (CL/F) and apparent volume of distribution (Vz/F) for E2609. Derived exposure parameters such as steady state area under the concentration time curve (AUC) and average concentration ($C_{avg}$) of E2609 and other derived parameters will be calculated from the model using the individual estimates parameterized for oral clearance and dosing history. (revised per Amendment 04)

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). The percentage change from baseline in CSF Aβ(1-x), Aβ(1-40), Aβ(1-42), t-tau, p-tau, and BACE1 variables (eg, activity and protein levels) after at least 4 weeks and at 18 months will be analyzed and presented graphically. (revised per Amendment 04) Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status. Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels, amyloid load on PET, vMRI and E2609 dose, plasma and CSF exposure will be initially explored graphically and any emergent relationship will be explored through population PK/PD modeling. Additionally, the relationship between CSF exposure to E2609 and the derived ADCOMS at 18 months, and the relationship between CSF exposure to E2609 and the change from baseline for 18 months in the ADAS-cog, the CDR, and the MMSE will be explored graphically. (revised per Amendment 04)

Additionally, the relationship between plasma exposures of E2609 and select lymphocyte parameters will be explored graphically, and any emergent relationship will be explored using population-based modeling methods. (revised per Amendment 04)

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. Further information is in the "Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments" section. Details of pharmacogenomic testing may be provided and reported separately.

**Safety Analyses**

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, and vital sign measurements will be summarized by treatment group using descriptive statistics.

<u>Lymphocyte Subsets</u>

Lymphocyte subsets, including but not limited to, CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages]) and regulatory T cells

will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose.

Serum IgG, IgM, IgA will be measured and summarized in the same manner as other laboratory parameters. (revised per Amendment 04)

**Interim Analyses**

In order to make decisions about the remainder of the study as well as the full E2609 clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. Investigators, other clinical site staff, subjects and caregivers/informants will remain blinded to study treatment. (revised per Amendment 03)

An interim safety analysis will also be conducted when the Stage A subjects (n=60, ±20%) have completed 12 weeks of treatment (or discontinue study drug early). (revised per Amendments 01, 03, and 04)

***The MCI/Prodromal Cohort***

Oversight of the Bayesian interim analyses and response adaptive randomization will be conducted by an independent committee that has expertise with Bayesian adaptive design in clinical studies. An unblinded external independent analysis group will provide the interim analysis outcomes to the committee at each interim analysis. The committee will ensure the integrity of the interim analysis and response adaptive randomization process through review of efficacy data. In addition, the committee will act in an independent advisory capacity to monitor the Bayesian interim analysis outcomes according to the early success and futility boundaries prespecified in the protocol. The committee will not be charged with any subject safety issues; this will remain the responsibility of the DSMB. The DSMB will continue to monitor the safety aspects of the study throughout Stage A and Stage B. The study may be stopped for safety at any time.

The first Bayesian adaptive interim analysis will be conducted when 100 MCI/Prodromal subjects have been randomized into the study (ie, including MCI/Prodromal subjects from both Stage A and Stage B). (revised per Amendment 01) Further interim efficacy analyses will be conducted after each additional 50 MCI/Prodromal subjects have been randomized, up to a maximum of 500 MCI/Prodromal subjects (ie, at 100, 150, 200, 250, 300, 350, 400, 450, 500 subjects randomized). If the study reaches full randomization, additional interim analyses will be conducted every 3 months until all subjects complete 18 months of treatment. The study will be monitored for futility at each interim analysis. Starting at the 200 subjects' interim analysis, the study will be monitored for success at each interim analysis. Each interim analysis will be conducted on data for the derived ADCOMS.

If the predefined early success criteria are met during the recruitment period, further recruitment and enrollment of MCI/Prodromal subjects into the study will stop (following confirmation from the Sponsor's Senior Management) and all currently randomized subjects will complete the full 18 months of treatment. No further interim analyses will be conducted after achieving early success.

If the predefined threshold for futility is reached, no additional subjects will be randomized into the study and the treatment of subjects already randomized into the study will stop and the study will be declared as "failed". All subjects will be monitored for safety for 3 months following their last dose.

If neither early success nor futility is reached and the study reaches full randomization, all subjects will complete 18 months of treatment. Interim efficacy analyses will be conducted every 3 months after full randomization is reached to assess futility and early success until all subjects complete 18 months of treatment. After full randomization, all study subjects will stop treatment only in the

event of futility.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

A group sequential design will be used for the Mild to Moderate AD cohort. This design includes 3 looks, 2 interim looks (when 60% and 80% information fractions are achieved) and 1 final look. Interim analyses will be performed after the MCI/Prodromal cohort crosses the early success boundary. The corresponding efficacy boundaries will be 0.076, 0.022, and 0.0423 for the first, second, and final analyses, respectively. If the actual information fraction during the interim analyses is different from 60% or 80% at the interim, the efficacy boundaries will be adjusted based on the actual information fraction. If early success in the MCI/Prodromal cohort is not achieved before the final analysis that is performed when all subjects have completed 18 months treatment, then only a final analysis will be performed in mild to moderate AD subjects. In the event of futility in the MCI/Prodromal cohort, an analysis will be performed for the Mild to Moderate AD cohort based on the data for mild to moderate AD subjects available at that time. (revised per Amendment 01)

**Adaptive Randomization in the MCI/Prodromal Cohort**

Randomization to placebo or 1 of 3 dose groups of E2609 will be fixed for the first 100 MCI/Prodromal subjects randomized in the study (1:1:1:1; placebo to each of the 3 active doses for the first 100 MCI/Prodromal subjects randomized, including those randomized from both Stage A and Stage B). Thereafter, randomization probabilities to each treatment group will be updated at each interim analysis, such that the randomization probability will be increased for the placebo group and dosage groups that represent the potential target dose ($ED_{90}$), and simultaneously decreased for other active arms. (revised per Amendment 01)

**Randomization in the Mild to Moderate AD Cohort** (revised per Amendment 01)

In Stage A, the mild to moderate AD subjects will be randomized to placebo or 1 of 3 E2609 dose groups (5, 15, and 50 mg of E2609) at a 1:1:1:1 ratio, while in Stage B, the mild to moderate AD subjects will be randomized to placebo or 1 of 2 E2609 dose groups (15 and 50 mg E2609) at a 1:1:1 ratio. (revised per Amendment 01)

**Stratification** (revised per Amendment 01)

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

**Sample Size Rationale**

***Sample Size Rationale in the MCI/Prodromal cohort***

Primary endpoint – derived ADCOMS: The sample size and design characteristics to test the hypothesis for the primary objective based on the primary endpoint were determined by means of simulations. Extensive study simulations have shown that a total of 500 subjects will be sufficient to demonstrate that the most likely $ED_{90}$ dose achieves a 25% improvement over placebo with a probability of at least 80% in the interim and final analyses. There is at least a 90% probability of study success for the dose response scenarios where treatment was considered to have a clinically meaningful treatment effect. Simulations have also shown that if there is no obvious dose effect, the probability of falsely claiming superiority to placebo is at most 5%.

For each of the 4 treatment groups (3 active doses and placebo), the final number of subjects per group will differ depending on the observed interim treatment responses.

vMRI: The null hypothesis is that there is no difference between active dose and placebo. There are 3 null hypotheses corresponding to 3 active doses. The alternative hypothesis is that at least 1 null hypothesis is false (1-sided). The null hypotheses will be tested using Dunnett's method with 1-sided alpha of 0.05. The statistical power was estimated through simulation for a moderate dose-response assumption that the percent reduction in change from baseline of total hippocampal volume compared with placebo would be 15%, 20%, and 25% corresponding to the 3 doses, respectively. The estimated power for actual planned study sample size is 78% at 18 months assuming an attrition rate of 20% at 18 months. Under a stronger dose-response assumption (ie, the percent reduction in change from baseline of total hippocampal volume compared with placebo is twice as much as that in the moderate dose-response assumption), the estimated power is at least 99% at 18 months.

Amyloid PET: The null and alternative hypotheses and statistical test are the same as those for vMRI. To estimate the sample size for the amyloid PET imaging subgroup at 18 months, a common SD of change from baseline was estimated at 0.33 and a reasonable mean difference between treatment and placebo was estimated as 0.25 (standardized uptake value ratio [SUVR]). Assuming a moderate dose-response, the best dose would achieve a difference of 0.25 (SUVR) and the middle and low doses would achieve a difference of 0.2 and 0.15 (SUVR), respectively, it would require a total of 100 subjects from all 4 arms at 18 months to achieve 80% power.

***Sample Size Rationale for the Mild to Moderate AD Cohort*** (revised per Amendment 01)

ADCOMS at Month 18: The null hypothesis is that there is no difference between active dose and placebo. There are 2 null hypotheses corresponding to 2 active doses. The alternative hypothesis is that at least 1 null hypothesis is false. The null hypotheses will be tested using Dunnett's test with 2-sided alpha of 0.05 as described for the Mild to Moderate AD cohort in the secondary analysis section. The statistical power was estimated through simulation for the dose-response assumption that the percent reduction in change from baseline of ADCOMS at 18 months compared with placebo would be 33% and 50% corresponding to the 2 doses, respectively. The estimated power for the actual planned 200 mild to moderate AD subjects is approximately 80% assuming a 2-sided alpha of 0.05. (revised per Amendment 01)

# 3 TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES



## LIST OF IN-TEXT FIGURES



## LIST OF APPENDICES

# 4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| Aβ | amyloid β |
| Aβ(1-x) | amyloid β (1-x) (ie, the amyloid β monomer from amino acid 1 to x [eg, 1-42]) |
| AChEI | Acetylcholinesterase inhibitor |
| AD | Alzheimer's disease |
| ADAS-cog | Alzheimer's Disease Assessment Scale - cognitive subscale |
| ADCOMS | Alzheimer's Disease Composite Score |
| AE | Adverse Event |
| ApoE | Apolipoprotein E |
| AUC | area under the concentration x time curve |
| $AUC_{(0\text{-}24h)ss}$ | area under the concentration x time curve at steady state from time zero to 24 hours |
| BACE1 | Beta-amyloid converting enzyme 1 |
| BP | blood pressure |
| bpm | beats per minute |
| CBB | CogState Brief Battery |
| CBC | complete blood count |
| CBP | childbearing potential |
| CDR | Clinical Dementia Rating |
| CES2 | carboxyesterase-2 |
| CFR | Code of Federal Regulations |
| $C_{max,ss}$ | maximum plasma concentration at steady state |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| CI | confidence interval |
| CRA | clinical research associate |
| CRF | case report form |
| CRO | contract research organization |
| CSF | cerebrospinal fluid |
| $C_{ss,av}$ | average steady-state concentration |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CTA | Clinical Trial Agreement |
| CYP | cytochrome P450 |
| $d_{Max}$ | Maximum effective dose |
| DSMB | data safety monitoring board |

| Abbreviation | Term |
|---|---|
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| ED | early discontinuation |
| $ED_{90}$ | lowest effective dose that achieves 90% of the greatest treatment effect |
| ELISA | enzyme-linked immunosorbent assay |
| FAQ | Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire) |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FLAIR | fluid-attenuated inversion recovery |
| GCP | Good Clinical Practice |
| GDS | Geriatric Depression Scale |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |
| HCVAb | hepatitis C virus antibody |
| HSV | herpes simplex virus |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ID | identifier |
| IEC | Independent Ethics Committee |
| Ig | immunoglobulin (eg, IgA, IgG, IgM) |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISLT | International Shopping List Task |
| IxRS | interactive voice and web response system |
| LLN | lower limit of normal |
| LNH | low/normal/high |
| LP | lumbar puncture |
| MAD | multiple ascending dose |
| MCI | mild cognitive impairment |
| MCI/Prodromal | Mild Cognitive Impairment due to Alzheimer's Disease/ Prodromal Alzheimer's Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mild to moderate AD | mild to moderate dementia due to Alzheimer's Disease |
| miRNA | micro-ribonucleic acid |

| Abbreviation | Term |
|---|---|
| MMRM | mixed-effects model with repeated measures |
| MMSE | MiniMental State Examination |
| MRI | magnetic resonance imaging |
| NAT2 | N-acetyltransferase 2 |
| NIA-AA | National Institute on Aging-Alzheimer's Association |
| OF | O'Brien-Fleming |
| PBMC | peripheral blood mononuclear cell |
| PD | Pharmacodynamic(s) |
| PET | positron emission tomography |
| PGx | pharmacogenomic(s) |
| PK | pharmacokinetic(s) |
| PP | per protocol |
| PRN | Pro re nata |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| p-tau | phosphorylated-tau |
| QD | once daily |
| QTc | corrected QT interval |
| QTcF | QTc interval calculated using Fridericia's formula |
| R | randomization |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reaction |
| SUVR | standardized uptake value ratio |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |
| TEMAV | treatment-emergent markedly abnormal laboratory values |
| t-tau | total tau |
| ULN | upper limit of normal |
| UNS | unscheduled |
| vMRI | volumetric magnetic resonance imaging |
| WHO DD | World Health Organization Drug Dictionary |
| β-hCG | beta-human chorionic gonadotropin |

# 5 ETHICS

## 5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA][s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigators or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

## 5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (CFR) (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

- European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved European Union member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

## 5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject and the identified caregiver or informant, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or understand it or if the identified caregiver or informant is unable to read, an impartial witness should be present during the entire informed consent discussion. If, in the Investigator's opinion, a subject lacks capacity to consent, the subject's assent should be obtained in addition to the written informed consent of a legal representative (capacity to consent and definition of legal representative should be determined in accordance with applicable local laws and regulations). (revised per Amendment 01) After the ICF and any other written information to be provided to subjects is read and explained to the subject and the identified caregiver or informant, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified caregiver or informant should also consent to supporting the subject's participation in the study and will be provided with a separate written ICF for his or her participation in the study, to be signed before he or she participates in any further aspects of the study.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified caregiver or informant must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified caregiver or informant will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified caregiver or informant should be

informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

All subjects will also be asked to provide written consent for cerebrospinal fluid (CSF) sampling at Baseline and after receiving study drug for 4 weeks and 18 months (or at Early Discontinuation). This consent for CSF sample collection is not required for study eligibility. (revised per Amendment 02)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects and will be via a separate, optional CSF consent form for the study. (revised per Amendment 04)

# 6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 35 investigational sites in the United States for Stage A and 125 sites globally for Stage B. (revised per Amendments 01, 02, and 04)

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

# 7 INTRODUCTION

At this time, there is no cure for Alzheimer's disease (AD), no known way of slowing down the progression of this disease, and no approved treatment available to reverse the deterioration. There is, therefore, an urgent unmet medical need for drugs that slow or prevent disease progression. Beta-amyloid converting enzyme 1 (BACE1) is a key enzyme responsible for the production of amyloid β (Aβ) peptides and plaque formation, and several reports have described elevated levels of BACE1 in AD brains (Coulson, et al., 2010; Lu, et al., 2012). Once amyloid plaques form, Aβ causes BACE1 levels to increase further, thus accelerating Aβ generation and plaque growth via a positive feedback loop. Therefore, BACE1 is a promising target for modifying or treating AD.

It is now widely accepted that mild cognitive impairment (MCI) due to AD and mild to moderate AD dementia are stages on a single disease spectrum, which follows an Alzheimer's pathological cascade. (revised per Amendment 01) Recent consensus papers from the international workgroups of the National Institute on Aging-Alzheimer's Association (NIA-AA), have endorsed this hypothesis (Albert, et al., 2011; Jack, et al., 2011; McKhann, et al., 2011; Rosen, et al., 1984; Sperling, et al., 2011).

From a clinical standpoint, demonstration of an effect on slowing disease course is hampered by the lack of sensitive tools for detecting relatively small changes in progression or treatment effect especially in early disease. In addition, drugs that are expected to slow disease progression require longer study durations to ensure adequate separation from placebo. These challenges have resulted in the use of biomarkers as surrogates for clinical effect in Phase 2 studies, in order to facilitate the development process for disease modifying agents. However, subsequent Phase 3 AD studies based solely on biomarker findings in Phase 2 have failed to show clinical effect, due, in part, to the fact that biomarkers may not predict clinical outcomes for potential disease modifying agents. These findings underscore the need for innovative approaches to clinical study design for measuring the effect of treatment.

E2609 is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, E2609 inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in cerebrospinal fluid (CSF) and plasma (rat, guinea pig, and monkey). In humans, E2609 has been shown to inhibit BACE1 enzyme activity in CSF and lower the levels of Aβ, including amyloid beta monomer from amino acid 1 to x (Aβ[1-x]), Aβ(1-40) and Aβ(1-42), in CSF both in vitro and in vivo. See the Investigator's Brochure for additional information. The target indication for E2609 is therefore treatment and disease modification of AD.

The present clinical study represents the sole Phase 2 study for the E2609 program, and is designed to establish Proof of Concept in subjects with Mild Cognitive Impairment due to Alzheimer's Disease/Prodromal Alzheimer's Disease (referred to as MCI/Prodromal throughout the protocol). The study also allows investigation of efficacy in subjects with mild to moderate dementia due to Alzheimer's Disease (referred to as mild to moderate AD throughout the protocol) to determine whether the effects of E2609 in this later stage population are comparable with those established in the MCI/Prodromal population within

this same study. (revised per Amendment 01) In the MCI/Prodromal population, Bayesian response adaptive randomization design is used with frequent interim analyses to continually update randomization allocation based on emerging clinical endpoint data. This approach allows for ongoing assessment of drug futility or evidence of early success and can mitigate the risks associated with larger and longer studies required to demonstrate clinical efficacy by leading to more efficient study termination or early advancement to a Phase 3 program. Results from this study will guide both the decision to move into Phase 3 development and the selection of the dose strengths to be taken into Phase 3. Moreover, this study is intended to be supportive for registration in the MCI/Prodromal population.

In the MCI/Prodromal population, this study will compare placebo and 3 oral doses of E2609 (5, 15, and 50 mg) administered once daily (QD) for 18 months. In the mild to moderate AD population, this study will compare placebo and 2 oral doses of E2609 (15 and 50 mg) administered QD for 18 months. To date, the longest duration of dosing with E2609 is 14 days (multiple ascending dose [MAD] Study E2609-A001-002 [Study 002]). (revised per Amendment 01)

This study (E2609-G000-202 [Study 202]) will comprise 2 stages: Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 in the United States sites only, before expanding enrollment to a larger and more global population of subjects in Stage B. This design will allow close monitoring of safety by an independent data safety monitoring board (DSMB), including a formal safety review as soon as the Stage A subjects (n=60, ±20%) have completed 12 weeks of treatment, have discontinued study drug or have withdrawn from the study. (revised per Amendment 04) The study also includes a number of exclusion criteria, specific blinded safety monitoring procedures and safety criteria for discontinuation of study drug in light of the preclinical and clinical safety data collected to date following administration of E2609.

## 7.1 Nonclinical and Clinical Safety Data

The toxicity of E2609 has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomologus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by E2609 in a clinical setting. Further details of the nonclinical data to date with E2609 can be found in the Investigator's Brochure.

The clinical program to date includes 6 Phase 1 studies:

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, single ascending dose (SAD) study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50-mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled MAD study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of E2609 and the PD effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of E2609. It also investigated the effects of E2609 on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [$^{14}$C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of E2609 under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) was a randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with E2609. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with E2609. In elderly subjects treated with 50 mg of E2609, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTc interval calculated using Fridericia's formula (QTcF) from baseline (14.9 msec at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of E2609 might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that E2609 altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary

infections or relapse of latent infections in subjects who received single doses of E2609. A single dose of E2609 up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, E2609 administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of E2609 on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP3A4] and carboxyesterase-2 [CES2]) increased by approximately 70% the area under the concentration × time curve (AUC) of E2609. Consequently, strong inhibitors of CY3A4 will be prohibited in this study.

Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of E2609. Therefore, no restrictions are required for the use of concomitant medications which are known to be inducers of CYP450 enzymes. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of E2609 when coadministered with E2609 but not when dosed at least 2 hours apart from E2609. E2609 (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of E2609. Therefore, on the basis of drug interaction considerations, the only restriction of concomitant medications is that for strong inhibitors of CYP3A4.

# 8 STUDY OBJECTIVES

## 8.1 Primary Objectives

The primary objectives are:

1. To evaluate the efficacy of daily dosing with 3 doses of E2609 compared with placebo by establishing the lowest effective dose that achieves 90% of the greatest treatment effect ($ED_{90}$) for E2609 on the derived Alzheimer's Disease Composite Score (ADCOMS) at 18 months of treatment in subjects with MCI/Prodromal
2. To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with mild to moderate AD (revised per Amendment 01)

## 8.2 Secondary Objectives

The secondary objectives are: (revised per Amendment 02)

1. To evaluate the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects, as measured by volumetric magnetic resonance imaging (vMRI)
2. To evaluate the efficacy of E2609 compared with placebo on the derived ADCOMS at 18 months in mild to moderate AD subjects (revised per Amendment 01)

## 8.3 Exploratory Objectives

(revised per Amendments 01,02, and 04)

The exploratory objectives are:

1. To explore the effect of E2609 compared with placebo on the derived ADCOMS following 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
2. To explore the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in mild to moderate AD subjects, as measured by vMRI
3. To explore the effects of E2609 compared with placebo on Aβ(1-x) and Aβ (1-42) in CSF after at least 4 weeks and at 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects
4. To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during post-treatment follow-up, in MCI/Prodromal and mild to moderate AD subjects, by assessment of:
    a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)

b. The Clinical Dementia Rating (CDR) scale
c. The Mini-Mental State Examination (MMSE)
d. The CogState Brief Battery (CBB)
e. The Functional Assessment Questionnaire (FAQ; (also known as the Functional Activities Questionnaire)
f. The International Shopping List Task (ISLT)

5. To explore the effects of E2609 compared with placebo on various biomarkers in MCI/Prodromal and mild to moderate AD subjects. Biomarkers to be explored include, but not limited to:
   a. CSF biomarkers of neurodegeneration (eg, tau, phosphorylated-tau [p-tau]) after 18 months of treatment
   b. Plasma and CSF amyloid, and CSF BACE1 measurements during 18 months of treatment and during post-treatment follow-up
   c. vMRI measurements including left and right hippocampal volume, whole brain volume, and total ventricular volume at 6, 12, and 18 months of treatment and during post-treatment follow-up
   d. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)
6. To characterize the population PK of E2609 in MCI/Prodromal and mild to moderate AD subjects, and to examine the effect of intrinsic and extrinsic factors (including N-acetyltransferase 2 [*NAT2*] phenotype) on the PK
7. To explore the relationship between the treatment effects of E2609 on the ADCOMS and its effects on CSF amyloid, CSF BACE1, CSF tau, and vMRI in MCI/Prodromal and mild to moderate AD subjects

# 9 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan

This study is a multicenter, placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild to moderate AD. (revised per Amendment 01)

A common set of inclusion criteria, consistent with the NIA-AA clinical research criteria for MCI due to AD or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study will be conducted in 2 stages, Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 (at least 12 weeks) before expanding enrollment to include a larger number of subjects in Stage B. All MCI/Prodromal subjects will be included in the primary efficacy evaluation irrespective of whether they were recruited into Stage A or Stage B. Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B. All mild to moderate AD subjects will be included in the efficacy evaluation of that cohort. (revised per Amendment 01)

Both Stage A and Stage B will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days, plus an additional window of up to 30 days if required [revised per Amendment 02]) will consist of a Screening Visit and a Baseline Visit. Screening assessments will be organized into 4 tiers; see Section 9.5.2.2, Table 6, and Figure 2.

All screening assessments must be completed, and eligibility to continue to the Baseline Period confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

In Stage A, all subjects (MCI/Prodromal and mild to moderate AD) will be randomized 1:1:1:1 to 4 treatment groups (E2609 at 3 doses or placebo). In Stage B, randomization of MCI/Prodromal subjects will start off at a 1:1:1:1 ratio (E2609 at 3 doses or placebo), until a total of 100 MCI/Prodromal subjects have been randomized. Remaining subjects in the MCI/Prodromal cohort will be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. Subjects with mild to moderate AD who are recruited in Stage B will be randomized in a 1:1:1 ratio to 3 treatment groups (E2609 at 2 doses or placebo). (revised per Amendment 01)

An overview of the study design is presented in Figure 1.

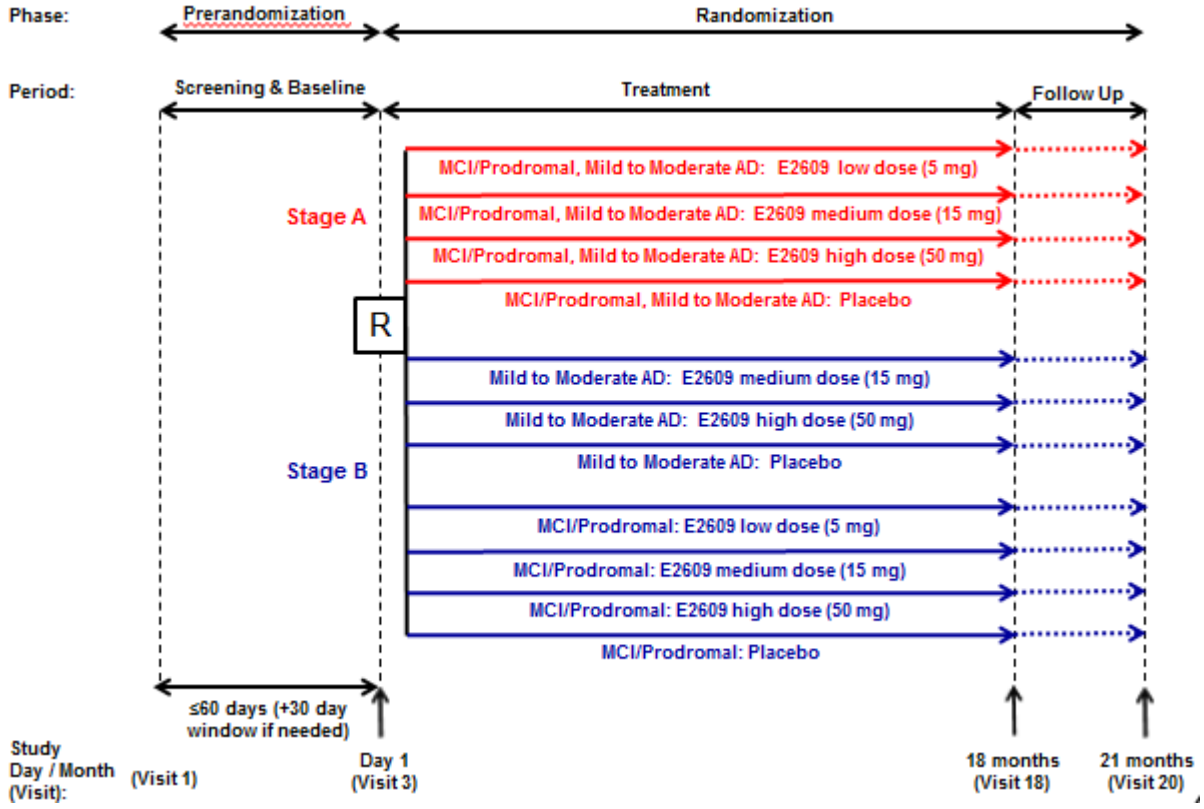



**Figure 1 Design of Study E2609-G000-202**

**(revised per Amendments 01 and 02)**

R = randomization, AD = Alzheimer's Disease, MCI = mild cognitive impairment.

**Stage A**

Stage A will be limited to approximately 35 sites in the United States. Stage A will randomize approximately 60 (±20%) eligible subjects at Visit 3, 1:1:1:1 to 4 treatment groups within each clinical cohort. There will be no Bayesian adaptation during Stage A. In addition to the placebo group, 3 doses of E2609 will be used to reduce CSF Aβ levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/PD modeling shows these doses should achieve these targets when administered QD with food and will be evaluated based on the 4-week assessment of CSF Aβ(1-x) from subjects who provide voluntary consent for CSF measurement (see Section 9.4.4 ). (revised per Amendments 01, 02, and 04)During Stage A, safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the 1st subject is randomized during Stage A, an independent DSMB (including at least 1 immunologist) will review all safety data in an unblinded manner. The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. Unless the DSMB recommends otherwise, randomization of subjects into Stage A will continue until approximately 60 subjects (±20%) have been randomized and dosed. (revised per Amendments 01 and 04)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

Interim analyses of the E2609 plasma PK for all subjects and the E2609 CSF PK and PD profiles will be performed on baseline data and samples collected after at least 4 weeks of study drug. These interim analyses, as well as analyses of safety data, will be performed on an ongoing basis throughout Stage A. Refer Section 9.7.3 for more detail. These data will be used to evaluate the CSF PD effects of E2609 doses, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels (see Section 9.4.4). The median and mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks or more of treatment for each dose of E2609 and the 90% confidence interval (CI) for the median will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline determined after at least 4 weeks of dosing. (revised per Amendments 01, 02, 03, and 04)

Once Stage A subjects have completed at least 12 weeks of treatment (or discontinued study drug early) an interim safety analysis will be conducted by Eisai and the DSMB. (revised per Amendments 01 and 04) Subjects in Stage A will continue study drug while the DSMB reviews all the available safety data, but randomization of additional subjects will not take place (ie, recruitment into Stage B will not commence) until the safety analysis is completed by the DSMB. At the time of this interim safety analysis, some subjects will have more than 12 weeks of safety data.

If there are safety signals with one of the E2609 dose groups that would require dose adjustment, changes to dose will be reflected in an amendment to the protocol. Similarly, if the interim PK/PD analyses demonstrate that further dose adjustment is required, changes to dose will be reflected in an amendment to the protocol. Information on how the data from these subjects will be handled in the statistical analysis will be described in the Statistical Analysis Plan. (revised per Amendment 04)

**Stage B**

Stage B will start after the DSMB safety review of Stage A has shown acceptable safety and tolerability of E2609 and after the doses of E2609 to be used in Stage B are evaluated. (revised per Amendment 02) Based on data from Stage A, the protocol will be reviewed and may be amended before beginning Stage B. Safety data from Stage B will continue to be reviewed by the DSMB (approximately every 3 months) until recruitment in the study is completed; following this the DSMB will meet approximately every 6 months.

Stage B will be conducted globally and will enroll, randomize, and dose additional eligible subjects up to a maximum of 500 MCI/Prodromal subjects and up to a maximum of 200 mild to moderate AD subjects. The final total number of MCI/Prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. (revised per Amendment 01)

In Stage B, both cohorts will include separate placebo groups. The MCI/Prodromal cohort will include 3 doses of E2609 (5, 15, and 50 mg QD), whereas the Mild to Moderate AD cohort will only include 2 doses of E2609 (15 and 50 mg QD). (revised per Amendment 01)

Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort during Stage B. Randomization of MCI/Prodromal subjects into Stage B will commence according to a fixed schedule (1:1:1:1; placebo:5 mg E2609:15 mg E2609:50 mg E2609) until a total of 100 MCI/Prodromal subjects (including those from Stage A) have been randomized. (revised per Amendment 01) The remaining subjects in the MCI/Prodromal cohort in Stage B will then be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. The mild to moderate AD subjects will be randomized according to a fixed schedule (1:1:1 placebo; 15 mg E2609; 50 mg E2609) throughout Stage B. (revised per Amendment 01)

Interim analyses are planned and are discussed in Section 9.7.3. (revised per Amendment 03)

### 9.1.1 Prerandomization Phase

The Prerandomization Phase includes a Screening Visit and a Baseline Visit. All Screening Visit assessments must be completed and eligibility to progress must be confirmed before any Baseline Visit assessments are performed. All Screening Visit and Baseline Visit assessments must be completed within 50 days (plus an additional window of up to 30 days if required [revised per Amendment 02]) and a window of no more than 10 days is to be observed between the completion of all Baseline Visit assessments (including confirmation

of eligibility following all Baseline Visit assessments) and randomization into the study at Visit 3 (revised per Amendment 02). Thus, the Prerandomization Phase will last for up to 60 days, plus an additional window of 30 days if required (revised per Amendment 02). The series of assessments conducted during this phase will determine eligibility for randomization into the study.

Inclusion criteria are discussed in Section 9.1 and detailed in Section 9.3.1. Before randomization, the clinician will provide a judgment on the classification of a subject as either MCI/Prodromal or likely mild to moderate AD. (revised per Amendment 01) This judgment may be discussed and reviewed with the Sponsor or Sponsor's representative, as necessary.

Results of the Screening safety magnetic resonance imaging (MRI) will be valid for 90 days from the date of scanning. Results of the lumbar puncture (LP) from subjects who voluntarily consent for CSF measurement will be valid for 90 days from the date of testing. Results of Screening PET scans conducted specifically for this study and for use in the longitudinal analyses will also be valid for 90 days from the date of scanning. These assessments will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. Historical PET scans used for determination of eligibility only (ie, not used for the longitudinal analyses) are valid for 12 months. (revised per Amendment 02)

#### 9.1.1.1 Screening Period

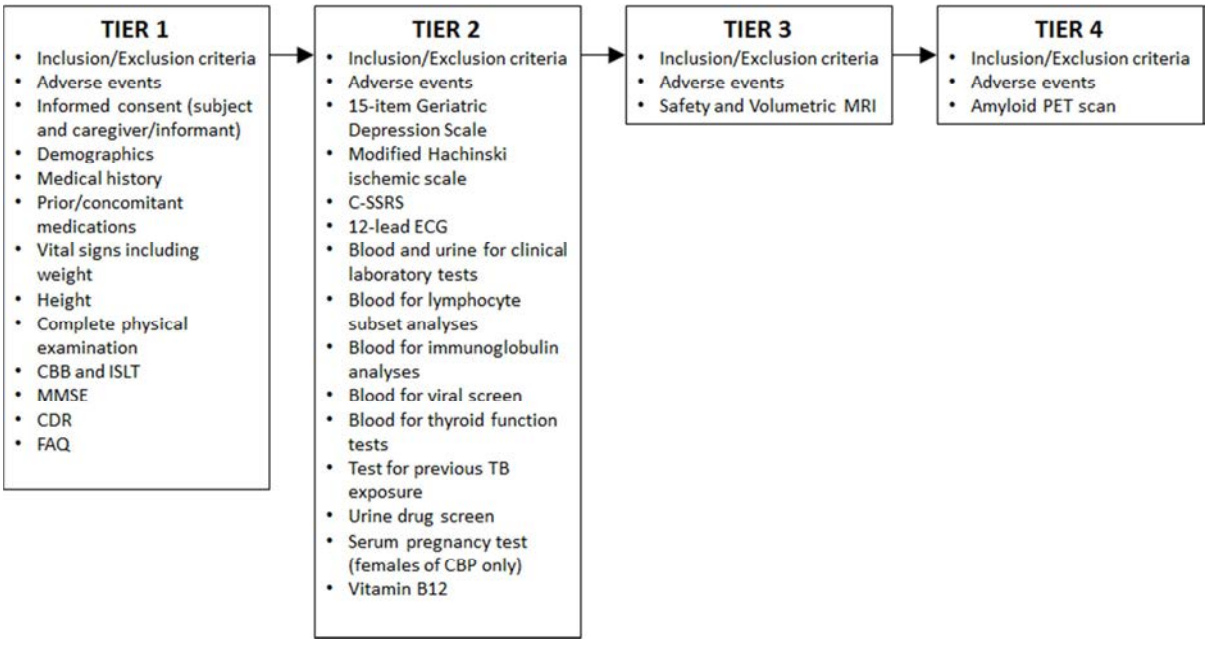
The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and caregiver or informant, and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained from both the subject and the caregiver or informant. The caregiver or informant needs to be present at this visit.

Study site personnel will interview the subject and caregiver or informant to obtain demographic and clinical information as described in Table 6, and will review inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2 and perform any required assessments in order to complete these criteria. Prior medications and medications currently being taken by the subject will be reviewed (see Section 9.4.7). The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

Clinical assessments for eligibility will be conducted during the Screening Visit as described in Table 6 and Figure 2.

Every effort should be made to conduct these assessments in the morning, but if this is not possible, they should be conducted at the same time of day at all subsequent visits. The screening assessments/procedures have been organized into 4 distinct tiers (Table 6 and

Figure 2). All assessments/procedures in each tier should be completed, and eligibility to continue screening in the study confirmed, before any assessments/procedures from the next tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures as long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. (revised per Amendment 01)




## Figure 2 Assessments to be Performed at Screening by Tier

CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), ISLT = International Shopping List Task (immediate and delayed recall), MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PET = positron emission tomography, TB = tuberculosis.

Cognitive assessments (Tier 1) are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). The recommended order of assessments at Screening is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. (revised per Amendment 02) The investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session (Tier 3).

Amyloid PET imaging will be used to confirm all subjects have amyloid deposition in the brain (Tier 4). An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. If an historical amyloid positive PET scan is being used, it should be submitted to the central PET reading group after the subject has completed and passed all Tier 1 assessments. (revised per Amendment 02)

#### 9.1.1.2 Baseline Period

All Screening Visit assessments must be completed (and eligibility to progress confirmed) before any Baseline Visit assessments are performed. The Baseline Visit assessments (per Table 6 and Section 9.5.1.2) are to be completed as soon as possible after completion of the final Screening Visit assessment (ie, PET scan) such that all Screening Visit and Baseline Visit assessments are completed within 50 days, plus an additional window of up to 30 days if required. (revised per Amendment 02)

Inclusion and exclusion criteria will again be reviewed, vital signs including weight will be recorded, and a 12-lead ECG will be conducted in triplicate. A routine physical examination will be conducted and a dermatological assessment and neurological examination (including the Brief Smell Identification Test [Sensonics Inc.]) will be performed. (revised per Amendment 04) A urine pregnancy test will be conducted for females of childbearing potential. Blood will be collected from all subjects for clinical chemistry and hematology, lymphocyte subset analyses, Ig analyses, and PD assessments. Blood samples will be collected and stored for determination of a subject's previous exposure to infective pathogens in the event of AEs that warrant further investigation occurring at a later point in the study. Psychometric assessments will be administered to the subject in the order stated in Table 6. The caregiver or informant needs to be present at this visit. The Columbia Suicide Severity Rating Scale (C-SSRS) will also be administered (Section 9.5.1.5.11).

For subjects who consent to CSF sample collection, a CSF sample will be obtained at this visit for PK and PD assessments (see Section 9.5.1.4). (revised per Amendment 02)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

Blood will be collected from all subjects for pharmacogenomic (PGx) analyses of apolipoprotein E (*ApoE*) and the *NAT2* phenotype of subjects enrolled in the study (see Section 9.7.1.7.2).

### 9.1.2 Randomization Phase

Subjects who complete the Baseline Visit assessments, and are eligible based on the inclusion and exclusion criteria (see Section 9.3.1 and Section 9.3.2), will begin the Randomization Phase no more than 10 days after completion of the Baseline Visit assessments and confirmation of the eligibility of the subject based on the results of all the Baseline Visit assessments (revised per Amendment 02).

The Randomization Phase will consist of a Treatment Period of 78 weeks duration and a Follow-Up Period of 12 weeks after the last dose of study drug.

#### 9.1.2.1 Treatment Period

Subjects will be randomized at the beginning of the Treatment Period and will receive study drug or placebo, to be administered orally QD with food. Double-blinding to study drugs will be in effect throughout the Treatment Period. The dose for a subject will not be changed during the study. However, dose adjustment for Stage B may be considered and subjects already randomized to a dose that needs to be adjusted will be switched to continue their treatment at the new adjusted dose.

Safety criteria for discontinuation of study drug are detailed in Section 9.3.3.

Subjects will attend the study site every week for the first 4 weeks after beginning study drug, then fortnightly until 12 weeks have elapsed since first dose. Visits will then be conducted at 16, 20, 26, 39, 52, 65, and 78 weeks after the first dose.

#### 9.1.2.2 Early Discontinuation

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug. (revised per Amendment 04)Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie. at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB and ISLT) will be conducted. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) after the Early Discontinuation Visit or within ±8 days of Follow-Up Visit 19 or Visit 20. Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above. (revised per Amendment 04)

#### 9.1.2.3 Follow-Up Period

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 4 post-treatment Follow-Up Visits: 2, 4, 8, and 12 weeks after the last dose of study drug. If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the post-treatment Follow-Up Period. (revised per Amendment 04)

The end of the study will be defined as the date of the clinical database lock (ie, when all study data are collected and data validation is completed).

As required by some regulatory agencies, the following estimates are provided:

- The study will begin in Nov 2014 and is projected to end by Oct 2019 (end date will depend on actual recruitment rate).
- The maximum estimated period for each subject on study is anticipated to be approximately 2 years.

## 9.2 Discussion of Study Design, Including Choice of Control Groups

### 9.2.1 Overview

The 2 stage design of the study allows for the safety and tolerability of E2609 to be assessed in a limited number of subjects (n=60±20%) before expanding recruitment into a larger population of subjects. (revised per Amendments 01 and 04)

The design of this study allows Proof of Concept to be established in subjects with MCI/Prodromal AD. The study also allows investigation of efficacy in subjects with mild to moderate AD to determine whether the effects of E2609 in this later stage population are comparable with those established in the MCI/Prodromal population within this same study (see Section 9.2.3 for discussion of the Bayesian design used in this study). (revised per Amendment 01)

Immunological and hematological parameters will also be assessed. (revised per Amendment 04)

The inclusion criteria for the MCI/Prodromal cohort will be consistent with the NIA-AA criteria for MCI due to AD (Albert, et al., 2011) and with the definition of Prodromal AD per Dubois et al., 2010 (see Section 9.2.2).

There is no active or positive control for this study as at this time, there is no cure for AD, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary efficacy tool for this Proof of Concept study is the composite scale ADCOMS (change from baseline in the derived ADCOMS at 18 months). The ADCOMS (Hendrix, et al., 2012) represents a novel composite approach integrating components of well-established tools (ADAS-cog, MMSE, and CDR) to improve sensitivity to disease progression and treatment effects in subjects with AD (Section 9.4.4).

Secondary efficacy endpoints include a biomarker of neuronal degeneration (shrinkage of neurons), which is the change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI; and a cognitive and functional assessment, which is the change from baseline in the derived ADCOMS at 18 months of treatment in mild to moderate AD subjects. (revised per Amendments 01 and 02) Exploratory endpoints including assessments of efficacy, safety and other biomarkers are also included.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups (Section 9.7.4) Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

The rationale for the selection of doses used in the study is provided in Section 9.4.4.

### 9.2.2 Rationale for Study Population

By the time AD progresses to dementia, with loss of functional capabilities, the amyloid load in the brain is approaching a plateau and significant neurodegeneration has occurred (Jack, et al., 2010). Consequently, there is a growing view within the AD field that it may be necessary to initiate disease modifying treatments earlier, before the onset of clinical dementia (Aisen, et al., 2010). However, this hypothesis remains to be demonstrated with clinically effective therapies, and may not apply to all therapeutic classes, it is possible that this consideration explains the failure of the humanized monoclonal antibody bapineuzumab (which targeted brain amyloid) to demonstrate clinical efficacy in late-phase studies in mild to moderate AD dementia. (revised per Amendment 01)

With this consideration taken into account, the primary clinical population of focus in this study is subjects with MCI/Prodromal AD. The mechanism of action of a BACE1 inhibitor where amyloid production is reduced means E2609 is more likely to be efficacious (ie, slow disease progression) the earlier in disease progression treatment is started, where limited neurodegeneration has occurred and associated clinical deficits are at a minimum. However, since the effect of BACE1 inhibition along the AD continuum remains to be characterized, E2609 will also be evaluated for its profile in mild to moderate stages of AD, in the event data emerge supporting its use beyond MCI/Prodromal AD. Indeed, recent data support the notion of continued progression of amyloid pathology even in these later stages of the disease (Hu, et al., 2015), although at a slower pace, suggesting a positive effect of BACE inhibition and amyloid beta reduction cannot be ruled out even in the later stages of the disease trajectory. Hence, in this study, E2609 will be assessed in subjects with disease states ranging from MCI/Prodromal to mild and even moderate AD. (revised per Amendment 01)

As discussed, efficacy is more likely to be observed in subjects with MCI/Prodromal AD but there is the possibility that efficacy will also be evident following administration of an amyloid modifying agents such as E2609 in subjects with more advanced disease such as mild to moderate AD. (revised per Amendment 01) For example, a study of tarenflurbil, a selective Aβ(1-42)-lowering agent, on cognition and function in subjects with mild to moderate AD showed the subjects with mild AD had lower rates of decline than those in the placebo group in activities of daily living and global function; however, slowing of cognitive decline did not differ significantly (Wilcock, et al., 2008). Similarly, differential effects on cognitive measures have been observed with solanezumab, where some benefit from treatment was observed in subjects with mild AD, although studies with solanezumab were considered to have failed to improve cognition or functional ability significantly (Doody, et al., 2014). Therefore, it is relevant to compare the effect of the BACE1 inhibitor E2609 in 2 different subject populations that differ in terms of AD severity before the initiation of large Phase 3 clinical studies. (revised per Amendment 01)

### 9.2.3 Rationale for the Use of Bayesian Adaptive Design

This study uses a Bayesian adaptive design for the MCI/Prodromal cohort only in Stage B. This design optimizes subject allocation and evaluation of efficacy in a smaller number of subjects by maximizing the number of subjects exposed to doses of interest. Frequent interim analyses will be performed to assess the probability of early success and futility and to aid in making early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis, such that subjects are more likely to receive a dose that is efficacious.

Subjects with mild to moderate AD will be assessed as a "nested" population that does not follow the Bayesian adaptive design. It was not considered appropriate to have a Bayesian design for both cohorts as this would have substantially increased the overall study sample size, delayed analyses of dose response, and would have added background "noise" for the comparison of subjects with MCI/Prodromal AD compared with those with mild to moderate AD. Data from each cohort will be analyzed independently for the purposes of decision making. A separate analysis of the 2 cohorts avoids the risk of data from subjects with mild to moderate AD confounding the results for the primary population (MCI/prodromal). (revised per Amendment 01)

### 9.2.4 Rationale for Clinical Endpoints

The ADCOMS (Hendrix, et al., 2012) was developed utilizing data from multiple studies to investigate responsiveness to progression and treatment effects rather than sensitivity to baseline deficits. The score was built empirically with no a priori assumptions, using a partial least squares regression model for placebo data from 4 MCI studies with a duration $\geq$12 months. A combination of cognitive and functional items was selected from a variety of well-established and validated scales that is most sensitive to change over time. The partial least squares regression coefficients from the model were used to form a weighted composite score comprising a total of 12 individual items taken from the ADAS-cog (4 items), the MMSE (2 items), and CDR (6 items), that assess both cognition and global function. Performance of the ADCOMS has been assessed against the original scales in several studies. The use of the ADCOMS allows for substantial sample size reductions in non-enriched and enriched MCI populations even over a 12-month period by increasing sensitivity. This derived score has shown adequate sensitivity in the MCI due to AD amyloid confirmed (CSF Aβ-positive) subgroup.

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007).

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975)

The CDR is a clinical global rating scale requiring the interviewing of both the subject and an informant who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The CBB is a brief, computer-administered cognitive test battery that requires approximately 10 minutes for administration (Darby, et al., 2012; Fredrickson, et al., 2008; Maruff, et al., 2009). The CBB has been used to detect cognitive impairment in several neurodegenerative conditions including the measurement of cognitive function in healthy older adults and in adults with clinically diagnosed AD and prodromal AD (Darby, et al., 2009; Hammers, et al., 2012; Lim, et al., 2012a; Lim, et al., 2012b). The administration, scoring, and reporting of the CBB is automated and highly standardized, resulting in cognitive paradigms that have been well-validated in neuropsychological and cognitive studies (Fredrickson, et al., 2008; Maruff, et al., 2009). See Section 9.5.1.3.1 for further details.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al,. 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials on the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson et al., 2011, Lim, et al., 2012a, Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with E2609 treatment.

Volumetric magnetic resonance imaging is discussed in Section 9.2.5.4.

### 9.2.5 Rationale for Biomarkers

#### 9.2.5.1 Overall Rationale

The biomarker strategy for this study includes the following aims:

- To establish an amyloid load in the brain at study entry (via the PET eligibility inclusion criterion)
- To evaluate safety (principally by MRI)
- To evaluate a PD effect in terms of both Aβ in CSF and brain amyloid assessed by amyloid PET and to establish that this PD effect is maintained long-term (revised per Amendment 02)

- To evaluate disease modification through longitudinal assessments of vMRI, amyloid PET, and CSF biomarkers of neurodegeneration (t-tau and p-tau)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

#### 9.2.5.2 Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect of E2609 on Aβ(1-40) +Aβ(1-42) and other C-terminally truncated Aβ peptides such as Aβ(1-38) through inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using [$^{11}$C]PiB, suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases in CSF Aβ concentrations that are seen in AD are believed to be related to this decrease in brain Aβ availability.

Both t-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni and Bhaskar, 2012). CSF tau measurements have been correlated with cerebral atrophy, while their ratios with Aβ42 have provided useful predictors of cognitive decline and progression to dementia due to AD. Rebalancing dysregulated amyloid production early in the process may positively affect the neurodegenerative process and thus affect these markers and benefit the disease trajectory. Therefore, monitoring these markers in conjunction with amyloid imaging may provide further supportive evidence of disease modifying effects. (revised per Amendment 04)

Baseline levels of Aβ(1-42), t-tau, and p-tau will also help elucidate the extent of AD pathology at entry to the study and can be combined with baseline levels of *ApoE4* genotyping in addition to the baseline imaging variables to help explain differences in treatment response.

The study will be stratified at randomization for *ApoE4* gene status in order to account for any *ApoE* status by treatment interaction or *ApoE* status by amyloid-related imaging abnormalities risk interaction.

#### 9.2.5.3 Amyloid PET

Amyloid PET imaging will be used in this study for 2 primary reasons: 1) to confirm the presence of AD pathology in the brain of subjects with MCI/Prodromal AD or mild to moderate AD at entry to the study; and 2) to evaluate the effects of E2609 on amyloid levels in the brain, both by whole brain analysis (the average of 5 to 6 cortical regions) and brain region analysis. (revised per Amendment 01)

Longitudinal amyloid PET imaging will be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug) as an exploratory measure of the potential disease-modifying effects of E2609. Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses) and will only be conducted until 18-month PET scans of acceptable quality have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used. (Revised per Amendment 02)

#### 9.2.5.4 vMRI

Volumetric imaging will be used to evaluate the effects of E2609 on rates of atrophy across the different dose groups and to provide support that effective treatment is associated with modification of disease course (secondary endpoint for the MCI/Prodromal population and exploratory endpoint for the mild to moderate AD population). (revised per Amendment 01) A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. Clinically efficacious doses are predicted to be associated with a slowing in the rate of hippocampal atrophy compared with rates observed in the placebo and non-efficacious dose groups. Treatment effects on left and right hippocampal, whole brain, and total ventricular volumes are exploratory endpoints.

Annualized rates of change of 2% to 3% have been reported for the AD brain compared with 1% in MCI and <1% in age-matched controls (Hua, et al., 2010, Leung, et al., 2010). However, subjects with MCI due to AD-dementia (CSF Aβ <192 pg/ml or positive amyloid imaging) show rates of atrophy comparable to those observed in subjects with AD-dementia (Hua, et al., 2009; Hua, et al., 2010; Leung, et al., 2010; Morra, et al., 2009), supporting the notion that such subjects are on similar trajectories as those with mild AD-dementia. Lower levels of CSF Aβ42, amyloid positivity on PET imaging, and higher levels of CSF t-tau in addition to the presence of the *ApoE4* allele have all been associated with greater rates of brain atrophy (Fjell, et al., 2010a; Fjell, et al., 2010b) and will be entered as covariates in various analyses. Hippocampal atrophy has also been shown to predict clinical progression independently of amyloid levels in the brain (Jack, et al., 2010), and this measure will be entered as a covariate in the analysis of the clinical endpoints along with the aforementioned variables.

Brain volume (total ventricular volume, whole brain, temporal lobe) generally shows a modest correlation with performance on a number of cognitive scales (Hua, et al., 2009; Hua, et al., 2010; Freeborough, et al., 1997; Leung, et al., 2010). Using volumetric analysis performed at 6-month intervals, these relationships and the effects of E2609 treatment will be explored further. Recent advances in analysis software have made structural imaging more sensitive to detect small changes and able to reliably measure rates of atrophy at these intervals, particularly in the posterior parietal and the lateral temporal regions during the early stages of disease (Hua, et al., 2009; Hua, et al., 2010). Given these observations, a demonstration of significant slowing or stabilization in the rate of atrophy in response to treatment, compared with placebo, will offer further support for disease modification.

### 9.2.6 Clinical Risks and Mitigation Strategy

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, and to mitigate clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. These safety aspects include the following:

- Two-stage study design: there will be a pause in recruitment after approximately 60 subjects (±20%) have been randomized to study drug (Stage A). Only after the safety of E2609 in these Stage A subjects (consisting of up to 12 weeks data for the later subjects and longer dosing periods for the earlier subjects) has been reviewed by the DSMB and considered acceptable, will randomization of further subjects into the study commence (Stage B). (revised per Amendments 01 and 04)
- Immunology-related and infection-related exclusion criteria
- Review of unblinded safety data by an independent DSMB at regular intervals
- Safety criteria for discontinuation of study drug based on CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cell) and other lymphocytes (absolute counts and percentage change from baseline), skin rash, reoccurrence of herpes virus infections including any oral herpes, genital herpes or shingles, other infections, MRI changes, ECGs, and pregnancy.

In addition to the features above, other safety aspects of this study designed to mitigate clinical risk include the following:

- Blinded safety data will be monitored by Eisai at regular intervals during the course of the study
- Routine safety assessments will include the monitoring and recording of all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events. To assess potential

immunomodulatory effects, peripheral blood mononuclear cells (PBMCs) will be collected at baseline, during treatment, and post-treatment.

As per the communication from the Food and Drug Administration (FDA) in Aug 2013, there are concerns that hypopigmentation of the skin and mucous membranes may occur with BACE1 inhibitory drugs. Although no such effects have been seen with E2609 to date, assessments by a reviewing dermatologist will be performed at regular intervals during the study. These assessments will be made centrally, using standardized photography and will specifically include evaluation of any areas of depigmentation or any rash. Dermatological assessments will be supplemented with a specific question to subjects regarding skin changes at each visit. Any such changes could be referred to the central reviewing dermatologist, and to a local dermatologist if needed, for further evaluation. See Section 9.5.1.5.8 for further details.

- Baseline and on-study blood and DNA samples will be taken and stored for all subjects, and CSF samples will be taken and stored for all subjects who consent to CSF sample collection (revised per Amendment 02). These samples may be tested in the event that a subject develops AEs that warrant further investigation (eg, if a subject develops a treatment-emergent infection) (see Section 9.5.1.2.2).
- Central reading of safety brain MRI assessments (including any MRI evidence of demyelination) will be performed at Screening, at approximately 6-month intervals during the Treatment Period, and at the final Follow-Up Visit.
- Full neurologic examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. Details of the neurologic examination are given in Section 9.5.1.5.9.
- Cognitive decline will be assessed as a safety assessment (ADAS-cog$_{14}$, MMSE, and CBB). Of particular importance will be the assessment of reaction time testing using the detection and identification tasks on the CBB.
- An assessment of suicidality using the C-SSRS will be performed at Screening, Baseline, and at regular intervals during the Treatment and Follow-Up Period (see Section 9.5.1.5.11).
- All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will have at least 4 off-treatment Follow-Up visits (2, 4, 8, and 12 weeks after the last dose of study drug). More frequent safety assessments can be made as unscheduled assessments/visits during the off-treatment Follow-Up period, if clinically indicated. (revised per Amendment 04)
- An ophthalmic examination will be conducted at Baseline and if the subject experiences visual disturbances during the course of the study (see Section 9.5.1.2.1).

## 9.3 Selection of Study Population

Stage A will randomize approximately 60 (±20%) eligible MCI/Prodromal or mild to moderate AD subjects at approximately 35 sites in the United States (revised per Amendments 02 and 04). There will be no restriction to the number of subjects from either

population. Stage B will randomize subjects at approximately 125 sites globally. Recruitment will continue in Stage B until a maximum of approximately 500 MCI/Prodromal subjects and up to a maximum of approximately 200 mild to moderate AD subjects have been randomized (including subjects randomized during Stage A). The final total number of MCI/prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. The number of mild to moderate AD subjects randomized in Stage B will depend upon the number of mild to moderate AD subjects randomized during Stage A. (revised per Amendment 01)

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

### 9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD (Albert, et al., 2011) or AD dementia (McKhann, et al., 2011) and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at Screening Visit 1:**
(revised per Amendment 02)

   a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation
   b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT. Alternatively, cognitive impairment of at least 0.5 SD from age-adjusted norms in delayed recall on the ISLT plus impairment of at least 1 SD from age-adjusted norms in at least 1 other computerized learning and memory test (ISLT immediate recall, or 1 of the learning and memory components of the CBB). (revised per Amendment 02)
   c. FAQ ≤24 (revised per Amendment 01)
   d. MMSE ≥16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading; an historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group (revised per Amendment 02)
3. Male or female, age 50 to 85 years, inclusive at time of consent
4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant

need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.

5. If receiving acetylcholinesterase inhibitors (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the Baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.
6. Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization

### 9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or MRI
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and <1cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could, in the opinion of the investigator, confound the MCI/Prodromal or

mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendments 01 and 02)

7. A score of ≥8 on the 15-item Geriatric Depression Scale (GDS) at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the LLN for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
12. Any contraindications to LP for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity). Only applicable to subjects consenting to CSF sample collection (revised per Amendment 02)
13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of Ig deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization.
20. Any active infection within the last 4 weeks prior to randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary

disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.

b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.

c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).

22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below population-adjusted LLN at Screening or Baseline and confirmed by a repeat test conducted 1 week after the initial test. The population-adjusted LLN for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are 396, 157, and 74 cells/µL respectively. See Appendix 5. (revised per Amendment 02)

23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the Investigator and the Medical Monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of clinical immunodeficiency. The discussion with the Medical Monitor should include a detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)

24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline

25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate ECGs. A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.

26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator

27. Left bundle branch block at Screening or Baseline

28. Persistent heart rate <50 or >100 beats per minute (bpm) at Screening or Baseline

29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening

30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)

31. Type 1 or Type 2 diabetes mellitus that is not well controlled

32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.

33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo). Diagnosis of an underlying disease causing hypopigmentation is not necessary for exclusion if the clinical presentation is consistent with such a condition. Hypopigmentation associated with scarring need not be exclusionary. (revised per Amendment 02)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the C-SSRS suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized

partner with confirmed azoospermia) throughout the entire study treatment period or for 28 days after study drug discontinuation.

- Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.
- Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
- (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]). (revised per Amendment 04)

### 9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may discontinue study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to stop study drug or withdraw from the study at any time for any reason.

Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). Follow-Up Visits will also be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug (see Section 9.1.2.3). Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie, at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB and ISLT) will be conducted. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) after the Early Discontinuation Visit or within ±8 days ofFollow-Up Visit 19 orVisit 20. Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above. (revised per Amendment 04)

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the Subject Disposition eCRF page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study drug and withdraws from the study at the same time, the ED Visit will be followed (see Section 9.5.5).

Safety-related criteria for discontinuation of study drug include the following:

a. A study drug discontinuation threshold will be set based on absolute counts of CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells). The discontinuation threshold will be set at below the level of the population-adjusted LLN (CD4=396 cells/μL; CD8=157 cells/μL; and CD19=74 cells/μL), at a level that represents a greater risk of opportunistic infection in the treated population. (revised per Amendment 02) For CD4 (T helper cells) the discontinuation threshold is 250 cells/μL. For CD8 (cytotoxic T cells) and CD19 (B cells) the discontinuation thresholds are 150 cells/μL and 50 cells/μL, respectively. Any subject who has CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below the discontinuation threshold as confirmed by a repeat test conducted within 1 week of the initial test but who has no clinical signs or symptoms of infection, will have study drug temporarily suspended for at least 2 weeks but no more than 4 weeks. During this period of study drug suspension, lymphocyte subset counts and complete blood count (CBC) with differentials will continue to be tested weekly until CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) have all returned to greater than the population-adjusted LLN after which time study drug can be resumed. Testing of lymphocyte subset counts and CBC with differentials is required weekly for 4 weeks following resumption of study drug administration. Temporary suspension and rechallenge with study drug is only permitted once for any given subject. If the lymphocytes and CD counts do not return to greater than the population-adjusted LLN within 4 weeks from the start of temporary suspension the subject will need to be permanently discontinued from study drug. (revised per Amendment 04)

b. Subjects with CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between the population-adjusted LLN and the discontinuation threshold will have lymphocyte subset counts performed on a weekly basis. (revised per Amendments 02 and 04) During the early stages of the treatment period, where visits are conducted weekly (ie, Visits 4, 5, 6, and 7), lymphocyte subsets are already scheduled to be measured on a weekly basis and so additional visits or blood draws are not required. (revised per Amendment 02) For these subjects, the decision as to whether the subject remains on study drug or is to be discontinued from study drug will be based upon clinical judgment and will take into account any clinical presentation in addition to the lymphocyte subset counts. These subjects may continue with treatment if there is no clinical evidence of infection. They will be discontinued from study drug if they have infections of a moderate to severe intensity (eg, subjects whose infections are not localized, or are systemically unwell, or who require systemic anti-infective drug treatment).

**Table 1 Study Drug Actions for Lymphocyte Subset Absolute Counts**

| Lymphocyte subset absolute counts | Action | Decision to continue, discontinue, or temporarily suspend study drug |
|---|---|---|
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold and no clinical signs or symptoms of infection | Retest within 1 week along with<br>CBC with differentials | If retest performed within 1 week confirms lymphocyte subset counts below the discontinuation threshold, temporarily suspend study drug for between 2 and 4 weeks. Continue weekly testing of lymphocyte subsets and CBC with differentials. Rechallenge with study drug allowed when CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts all greater than population-adjusted LLN. Temporary suspension and rechallenge permitted only once for each subject. |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between population-adjusted LLN and discontinuation threshold | Lymphocyte subset counts (and CBC with differentials) to be performed weekly until lymphocyte subset counts return to ≥ population-adjusted LLN | Decision will be based upon lymphocyte subset counts and clinical judgment |

LLN = lower limit of normal, CBC = complete blood count.

(Table revised per Amendments 02 and 04)

c. Subjects with clinical evidence of infection will have their CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts measured. Blood and other biological samples will also be collected for investigations of infective pathogens (eg, serological tests, quantitative polymerase chain reaction, microscopy, and culture) where appropriate. In subjects with infection, if any of their absolute cell counts meets the discontinuation thresholds, study drug will be discontinued. All subjects with severe infections will be discontinued from study drug. All subjects with herpes zoster (shingles) or ocular herpes infections will be discontinued from study drug, regardless of severity of presentation. Subjects with mild or moderate infection may continue treatment with study drug unless otherwise clinically indicated or otherwise specified below. Specifically, when any of the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are between the population-adjusted LLN and the discontinuation thresholds, subjects with infections of moderate intensity will be discontinued from study drug (eg, subjects whose infections are not localized, or subjects who are systemically unwell, or who require systemic anti-infective drug treatment). All subjects with infection who are discontinued from study drug will be followed for a period of 12 weeks or until the infection resolves/ stabilizes or until the CD4 (T helper

cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts have returned to greater than population-adjusted LLN (whichever comes latest). (revised per Amendments 02 and 04)

**Table 2 Study Drug Actions for Lymphocyte Subset Absolute Counts and Infection**

| Criterion | Severity of Infection | | | |
|---|---|---|---|---|
| | None | Mild | Moderate | Severe |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold | If confirmed with repeat testing within 1 week, then temporarily suspend study drug as per instructions above. | Discontinue study drug | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between population-adjusted LLN and discontinuation threshold | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts always > population-adjusted LLN | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated (See (e) for exception) | Discontinue study drug |

LLN = lower limit of normal.

(Table revised per Amendments 02 and 04)

d. A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (see (e) for exception), will be discontinued from study drug and a dermatological consult will be requested regardless of whether the rash is considered drug-related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatological consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

e. Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

f. Development of any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. If discontinued from study drug, subjects will undergo an ED Visit within 7 days after

discontinuation and will attend the Follow-Up Visits 2, 4, 8, and 12 weeks after the last dose of study drug. They will also undertake an Unscheduled Visit (with MRI) at approximately 4 weeks after the visit at which such MRI features were first identified. An MRI will also be performed at approximately the time of the final Follow-Up Visit (Visit 20). Additional visits for safety may be arranged if clinically indicated in the opinion of the investigator, including after 12 weeks after the last dose of study drug. At any time during the treatment period, subjects who have asymptomatic, treatment-emergent microhemorrhages as detected by MRI, but none of the features which merit discontinuation of treatment (ie, vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic treatment-emergent microhemorrhage) may continue with treatment. These subjects will have safety assessments (including MRI) at approximately 4 weeks after the visit at which such MRI features were found. They will also continue with the scheduled MRI scans. Additional unscheduled MRI scans may be arranged on an individual subject basis in discussion with the study medical monitor. (revised per Amendment 04)

g. A postdose ECG with an average QTcF interval >500 msec from triplicate ECGs

h. A postdose ECG with a QTcF interval increase from baseline >60 msec and a QTcF interval >450 msec as demonstrated from triplicate ECGs

i. Any seizure (motor or non-motor)

j. Pregnancy

## 9.4 Treatments

### 9.4.1 Treatments Administered

For this study the test drug is E2609 and the control drug is placebo. All study drugs are to be administered orally, QD, with food.

Treatments to be administered in Stage A and Stage B are shown below and in Figure 1.

The 2 highest E2609 doses (15 and 50 mg) taken into Stage B, after the PK/PD and safety review from Stage A, will be used for the mild to moderate AD population in Stage B. (revised per Amendment 01)

- Stage A: 3 doses (5, 15, and 50 mg) of E2609 or placebo
- Stage B, MCI/Prodromal Cohort: 3 doses (5, 15, and 50 mg) of E2609 or placebo
- Stage B, Mild to Moderate AD Cohort: 2 doses (15 and 50 mg) of E2609 or placebo. (revised per Amendment 01)

Study treatment will begin on Day 1 (at the study site) following Randomization and will continue for approximately 78 weeks. Please refer to Table 7 and Section 9.5.1.4.1 for specific information on drug administration on days when PK sampling is to be performed.

Study drug doses will remain the same for each individual subject unless the interim PK/PD analysis determines that an entire dose level requires adjustment (Section 9.4.4). See

Section 9.3.3 for safety-related discontinuation criteria of study drug. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

### 9.4.2 Identity of Investigational Product

E2609 tablets of 5-, 10-, and 25-mg dose strengths will be supplied. Placebo tablets of identical appearance will also be available. Each subject will receive 2 tablets, which combined will make up the required doses of E2609 5, 15, 50 mg, or placebo. The tablets will be supplied by the Sponsor in labeled blister packs. The product release certificates for E2609 and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either E2609 or placebo, or both (see Section 9.4.2.3 for labeling details).

#### 9.4.2.1 Chemical Name and Formula of E2609

- Test drug code: E2609
- Generic name: not applicable
- Chemical name: International Union of Pure and Applied Chemistry
- *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

#### 9.4.2.2 Comparator Drug

Not applicable.

#### 9.4.2.3 Labeling for Study Drug

E2609 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier (ID)

- Lot number/batch number
- Storage conditions, expiration date if necessary

#### 9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

### 9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used for Stage A (all subjects), for Stage B MCI/Prodromal subjects and Stage B for mild to moderate AD subjects are described in Section 9.4.1. (revised per Amendment 01)

Randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized blister card identification numbers. At enrollment, the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 3), the IxRS will assign each subject a unique randomization number.

### 9.4.4 Selection of Doses in the Study

It is not known how the level of CSF or brain Aβ reduction is related to clinical efficacy. Therefore, in this study, doses will be selected such that at steady state, they will result in 25%, 50%, and 75% reduction in CSF Aβ levels from baseline to cover a broad range of PD effects.

In Study 007, the relative bioavailability of a tablet formulation of E2609 in the fed and the fasted states compared with the capsule formulation in the fasted state (used in Studies 001 and 002) was investigated. It was found that when the tablet form of E2609 (50 mg) was administered with food, the exposure (ie, AUC) of the parent drug E2609 was higher, with lower maximum observed concentrations and reduced exposure to the metabolites, compared with either formulation in the fasted state.

Based on the PK/PD modeling using data from healthy volunteer Studies 001, 002, and 007, doses of 5, 15, and 50 mg QD administered as the tablet formulation with food in this study should achieve CSF Aβ reduction from baseline of approximately 25%, 50%, and 75% at steady state, respectively (Table 3).

**Table 3 Predicted Steady State Plasma PK Parameters and CSF Amyloid β Reduction From Baseline**

| E2609 Tablet Daily Dose (mg) With Food | E2609 Plasma $C_{max,ss}$ (ng/ml) | E2609 Plasma $C_{ss,av}$ (ng/ml) | E2609 Plasma $AUC_{(0-24h)ss}$ (ng.h/ml) | % Reduction CSF BACE1 Activity | % Reduction CSF Aβ(1-x) |
|---|---|---|---|---|---|
| 5 | 6.2 | 3.3 | 80.3 | 16.2 | 33 |
| 15 | 18.6 | 10 | 240.9 | 36.6 | 56 |
| 50 | 62.1 | 33.5 | 803.0 | 65.7 | 79 |

Aβ(1-x) = amyloid beta monomer from amino acid 1 to x, $AUC_{(0-24h)ss}$ = area under the concentration x time curve at steady state from time zero to 24 hours, BACE1 = beta-amyloid converting enzyme, CSF = cerebrospinal fluid, $C_{ss,av}$ = average steady-state concentration, $C_{max,ss}$ = maximum plasma concentration at steady state, PK = pharmacokinetics.

The PK/PD modeling described above, which was conducted using data obtained from healthy volunteers, has also been supported by modeling of data from subjects with an underlying AD pathology (Study 101). Furthermore, external data with another BACE1 inhibitor (MK-8931) showed a similar PD effect in AD patients as in healthy volunteers (Forman, et al., 2013). Therefore we are confident that the modeling of E2609 effects in healthy subjects will be applicable for both MCI/Prodromal and mild to moderate AD dementia patients. (revised per Amendment 01)

The exposure of the highest dose in this study (50 mg QD tablet administered with food) is less than that of the 100 mg QD dose (capsule administered fasted) in Study 002.

The 100 mg QD dose administered for 14 days in Study 002 was well tolerated with no clinically significant changes in laboratory parameters, vital signs, or ECG parameters. On Day 15, for the 100 mg QD cohort in Study 002, there was a reduction of CD4 lymphocyte counts compared with placebo (CD4 lymphocyte counts on E2609 decreased by 3.1% from baseline, whereas the placebo control showed an increase of 8.7%), but this decrease was less than that observed at doses of 200 mg (22.9% decrease) or 400 mg (17.3% decrease). No subject had infections or drug rash while receiving E2609 100 mg QD or at lower doses in Study 002, whereas at 200 and 400 mg QD, 4 subjects had symptomatic orolabial HSV1 relapses and 2 subjects at the highest dose had drug rash. The highest dose for Study 202 of 50 mg QD (tablet administered with food) is therefore expected to have a similar or better safety profile compared with the 100 mg QD capsule (administered fasted) in Study 002. Specific exclusion criteria, blinded and unblinded safety monitoring procedures, and safety criteria for discontinuation from study drug are included in this study in order to mitigate any immunology-related risk with E2609, particularly in light of the progression from 14 days of dosing (Study 002) to 18 months of dosing in this study.

In Stage A, all subjects will be randomized to receive either placebo or E2609 at 5, 15, or 50 mg QD. In Stage B, subjects in the MCI/Prodromal cohort will continue to be randomized to receive either placebo or E2609 at 5, 15, or 50 mg QD. In Stage B, subjects in the Mild to Moderate AD cohort will be randomized to receive either placebo or E2609 at 15 or 50 mg QD, but not the 5-mg QD dose. The rationale for not including an E2609 5-mg QD dose in the dose regimens for Stage B subjects with mild to moderate AD is that more

advanced disease may require greater reduction in CSF Aβ levels for comparable effects. (revised per Amendment 01)

Interim analyses of the E2609 plasma PK for all subjects and the E2609CSF PK and PD profiles will be performed on baseline data and samples collected after at least 4 weeks of study drug. These interim analyses, as well as analyses of safety data, will be performed on an ongoing basis throughout Stage A. Refer Section 9.7.3 for more detail. The median and mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment for each dose of E2609 and its 90% confidence interval for the median will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data from Stage A and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline after 4 weeks of dosing. (revised per Amendments 01, 02, 03, and 04)

If dose adjustment is required for Stage B, a protocol amendment reflecting the new doses will be submitted.

### 9.4.5 Selection and Timing of Dose for Each Subject

E2609 is administered orally, QD, with food. Study treatment will begin on Day 1 following randomization and will continue for approximately 78 weeks.

### 9.4.6 Blinding

E2609 and placebo will be administered as tablets of identical appearance.

During the Randomization Phase and Follow-Up Phases, subjects, caregivers/informants, and all clinical site personnel involved with the conduct and interpretation of the study, including investigators will be blinded to the treatment codes (double-blind). In order to make decisions about the remainder of the study as well as the full E2609 clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. (revised per Amendment 03)

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (ie, those who are trained and certified to perform the various cognitive assessments that are undertaken in this study). Furthermore, at the site, the notes and reports relating to safety assessments must be kept separate from the notes and reports relating to efficacy, particularly for the CDR. (revised per Amendment 01)

Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

The PK/PD interim analyses will take place throughout the study as per Amendment 03 and will be conducted by an independent PK/PD scientist at the sponsor. Any additional changes to dose required for this study will be reflected in a further amendment to the protocol and the Statistical Analysis Plan will detail how data will be handled in the primary analysis. (revised per Amendments 02 and 04)

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

At the conclusion of the study, all unused drug supplies are to be returned to the Eisai approved contract packaging vendor.

### 9.4.7 Prior and Concomitant Therapy

Medication (including over-the-counter medications) or therapy administered to the subject before the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2. Prohibited medications are presented in Listing 1 through Listing 5. Medications that are permitted with restrictions are listed in 6 through Listing 8. (revised per Amendment 04)

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit: (revised per Amendment 04)

- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization

- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization. However, during the treatment period of the study, short term (not more than 14 days) use of steroids up to the equivalent of prednisolone 40 mg once daily is permitted after discussion with the Medical Monitor. Dosing with study drug should be suspended from the time steroid treatment is started. Complete blood count and lymphocyte subsets should be determined prior to starting steroid treatment and continue to be monitored weekly. Study drug may be resumed after discussion with the Medical Monitor when the following conditions are met: (1) treatment with steroids has been completed for at least 1 week; (2) total lymphocytes not <LLN; (3) no lymphocyte subsets are below the discontinuation threshold; (4) the investigator considers that the medical condition which required treatment with steroids has improved or resolved. Weekly testing of lymphocyte subset counts and CBC with differentials is required for 4 weeks following resumption of study drug administration. (revised per Amendment 04)

Subjects taking AChEIs or memantine must meet the following criteria in order to be included in the primary analyses:

- On a stable dose for 12 weeks before the Baseline cognitive assessments at Visit 2
- Remain on a stable dose while on study

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for the primary analyses.

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed. Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before randomization. They may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 04)
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety, and are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks.

Antiplatelet therapy: (revised per Amendment 04)

- For subjects who consent to CSF sample collection: Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) are permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.
- For subjects who do not consent to CSF sample collection: Aspirin and clopidogrel, individually or in combination, are permitted.

### 9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period. CRAs will review treatment compliance during site visits and at the completion of the study.

### 9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the principal investigator including a copy of the principal investigator's current medical license (required for United States sites) or medical registration number on the curriculum vitae
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study

drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

## 9.5 Study Assessments

### 9.5.1 Assessments

#### 9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

#### 9.5.1.2 Baseline Assessments

Assessments to be made at Screening and Baseline and throughout the study are described in Section 9.5.1.3, Section 9.5.1.4, and Section 9.5.1.5.

##### 9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, current medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment due to AD. Subjects will be asked about history of TB, infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV Types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include onset, duration, relapse frequency, severity, and treatments. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The 15-item GDS and modified Hachinski ischemic scale will also be assessed at Screening as part of the exclusion criteria.

Physical examinations (complete or routine) will be performed as designated in Table 6. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, and skin, and a neurological examination (including the Brief Smell Identification Test [Sensonics Inc.]). (revised per Amendment 04). A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

##### 9.5.1.2.2 VIRAL TESTING

As specified in Table 6, blood will be collected for screening for Hepatitis B and Hepatitis C for determining eligibility, and at Baseline for viral characterization.

##### 9.5.1.2.3 B12 TESTING

Blood will also be collected for vitamin B12 levels as specified in Table 6.

#### 9.5.1.2.4 TB EXPOSURE TESTING

Blood will also be collected for testing for previous TB exposure, as specified in Table 6.

#### 9.5.1.2.5 URINE DRUG TESTING

Urine will be collected for drug screening as specified in Table 6.

### 9.5.1.3 Efficacy Assessments

#### 9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

The timing of psychometric assessments is shown in Table 6 and Table 7. These assessments should be administered in the morning (or, if not possible, consistently at the same time of day) and should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). At the Screening Visit, the recommended order of assessments is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. At the Baseline Visit, the assessments are to be conducted in the following order: MMSE, CDR, ADAS-cog$_{14}$, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). (revised per Amendment 02)

At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

**The Derived Alzheimer's Disease Composite Score:** The primary efficacy endpoint is the change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects.

The ADCOMS is derived from the ADAS-cog (4 items), the MMSE (2 items), and the CDR (all 6 items), described below. The ADCOMS is more sensitive to clinical progression compared with currently existing clinical batteries and requires smaller sample sizes for clinical studies in MCI/Prodromal AD or mild to moderate AD. (revised per Amendment 01) It also shows sensitivity to treatment effects with AChEIs. The ADCOMS assesses both cognitive and functional domains and can be offered as a single primary clinical endpoint. The ADCOMS has a range from 0 to 1.97.

**CogState Brief Battery:** The CBB is a computer-based battery comprising 4 cognitive tests:

- Detection – a simple reaction time test where the subject presses a key when the card is turned face up from a pack of cards ("Has the card turned over"). Speed of response is the measure.
- Identification – a simple choice reaction time test where the subject presses 1 of 2 keys when the card just turned face up is either a red card or a black card ("Is the card red"). Speed of response is the measure.
- One Card Back – a simple working memory test where the subject presses 1 of 2 keys when the card turned face up is either the card seen in the immediately previous trial or not ("Is the previous card the same"). Accuracy of response is the measure.
- One Card Learning – a visual learning and memory test where the subject presses 1 of 2 keys depending on whether the card just turned face up has been seen before or not in the task ("Have you seen this card before in this task"). Accuracy of response is the measure.

**ISLT:** The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 15 minutes, in which time the CBB is performed, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

**Mini Mental State Examination:** A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

**Clinical Dementia Rating:** The CDR assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

**Alzheimer's Disease Assessment Scale - cognitive subscale:** Discussed in Section 9.2.4.

**Functional Assessment Questionnaire:** The caregiver or informant provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent). (revised per Amendment 04)

#### 9.5.1.3.2 VOLUMETRIC MRI

Volumetric MRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the Alzheimer's Disease Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

Volumetric MRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. Volumetric MRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. Volumetric MRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 6 and Table 7, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

For subjects who consent to CSF sample collection, CSF samples will be collected by LP (gravity drip method) at the timepoints specified in Table 6 and Table 7 (revised per Amendment 02). The CSF sample taken at the Baseline Visit will only be performed after subjects consent to CSF sample collection, and after confirmation of an amyloid positive PET scan (revised per Amendment 02). See Section 9.5.1.4.2 for further details.

### 9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

#### 9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of E2609. For subjects who consent to CSF sample collection, CSF samples will be collected for the determination of E2609 concentrations. (revised per Amendment 02) Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with E2609.

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 6 and Table 7. Two PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visits 5, 11, 14, and 16, and 4 to 8 hours postdose at Visit 7 and Visit 18 (or at the ED Visit). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug with food at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or at the ED Visit) the PK blood sample should be collected shortly before or shortly after completing the LP. (revised per Amendment 01) Although the PK sampling procedures at the ED visit should follow those of Visit 18, in the event that study drug has already been discontinued prior to the ED visit, then no dosing will be conducted. However, a PK sample at trough (before LP) will be collected, followed by LP at approximately the same time as previous visits. A 2nd PK blood sample will be collected as close as possible in time to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

Blood will also be drawn where possible at the 1st report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

#### 9.5.1.4.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

**Biomarkers**

Subjects who consent to CSF sample collection will be encouraged to stay at the site after completion of LP for medical observation (revised per Amendment 02). At Baseline, a CSF sample will be collected by LP (gravity drip method) after fasting (preferred), or at least 2 hours after the most recent meal (Section 9.5.1.3.3). The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 [or later postrandomization timepoint] and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. (revised per Amendment 04) At visits where cognitive tests are also performed, if the tests are to be performed on the same day, the LP must be performed after the cognitive tests have been completed and the subjects should rest and drink some fluid to hydrate before the LP. (revised per Amendment 01) The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. The CSF sample will be used for PD assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 levels and activity. (revised per Amendment 04)

Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to

postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendment 04)

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The pre- and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendment 04) BACE1 levels will be measured using internally developed fluorescence resonance energy transfer and ELISA based assay(s). Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

The blood sample collected for PD analyses at Baseline should be collected on the same day shortly before or shortly after completing the LP at Baseline. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

At the Baseline Visit, blood samples will be collected and stored for determination of prior exposure to any suspected infective agents in the event that the subject develops treatment-emergent AEs that warrant further investigation (eg, treatment-emergent infection). For subjects who consented to CSF sample collection, CSF samples from the Baseline Visit will also be stored for the same purpose. (revised per Amendment 02) Testing may include, but not be limited to, serological tests, viral titer by quantitative polymerase chain reaction, or human leukocyte antigen genotyping.

Blood samples will be collected for PD assessments as specified in Table 6 and Table 7. See Section 9.5.1.4.2 for further details.

For all subjects, baseline and on-study blood samples, DNA samples, and any CSF samples collected from subjects who consent to CSF collection will be stored for up to 15 years. (revised per Amendment 02)

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

**Pharmacogenomics**

A blood sample will be obtained at Baseline and will be used to determine the *ApoE* genotype (homozygous or heterozygous E4 versus non-E4) and the *NAT2* phenotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response, safety, or PK of E2609. Details of which genotype / phenotype data will be applied to the analyses of efficacy, safety or PK will be discussed in the Statistical Analysis Plan.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the

development of AEs, or underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

**Amyloid PET**

An amyloid PET scan will be performed at Screening to confirm deposition of amyloid in the brain. An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02) Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses) and will only be conducted until acceptable 18-month PET scans have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used (Table 6). (revised per Amendment 02) PET scanning will be performed with a locally approved Aβ imaging agent (eg, Amyvid). Descriptions and detailed instructions for all imaging can be found in the imaging manual.

Amyloid PET imaging is an exploratory measure of the potential disease-modifying effects of E2609.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, lymphocyte subsets, Igs, and urine values; periodic measurement of vital signs and ECGs; performance of physical and neurological examinations; centralized dermatological assessments; the C-SSRS; and safety MRIs as detailed in Table 6 and Table 7 will also be conducted. Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and post-treatment for exploratory immunomodulatory and immune-based analyses.

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (see Section 9.4.6). (revised per Amendment 01)

##### 9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E2609.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: It is not necessary to report every sign or symptom as a separate AE if the overall disease [diagnosis] is being reported as an AE.)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, discontinuation of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 20, as shown in Table 7). For subjects who discontinue early from study drug but undertake further efficacy assessments, AEs will only be collected for 3 months after the last dose of study drug, ie, through to the final follow-up visit (Visit 20). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF. SAEs will be collected for 3 months after the last dose of study drug, ie, through to the final Follow-Up visit (Visit 20). For subjects who discontinue early from study drug but continue with further efficacy assessments, SAEs will be solicited only for 3 months after the last dose of study drug (ie, up to the final follow up visit [Visit 20]). However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures. (revised per Amendment 04)

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the ADAS-cog$_{14}$, MMSE, ISLT and CBB (see

Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 4.

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis
- Dissociative state

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.11 for a description of the C-SSRS).

The following AEs will require the collection of information sufficient to provide a detailed description of the event, treatment and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection; any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a "yes" answer to Type 4 or 5 suicidal ideation, or a "yes" response to any suicidal behavior on the C-SSRS.

All AEs must be followed through the final Follow-Up visit (Visit 20), or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. (revised per Amendment 04)

**Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.**

### Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

### Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

*Classification of Causality*

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

#### 9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reportable using the criteria of important medical event if the event does not meet other serious criteria: new onset seizures, ocular herpes.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the eCRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

#### 9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 4. Subjects should be in a seated or supine position during

blood collection. Table 6 and Table 7 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

See Section 9.3.3 for safety criteria for discontinuation from study drug related to absolute counts of CD4, CD8, and B lymphocytes, and for lymphocyte subset counts.

**Table 4 Clinical Laboratory Tests**

| Category | Parameters |
|---|---|
| **Hematology** | Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils).<br><br>PT, PTT, and INR (Screening and Baseline only) (revised per Amendment 02) |
| **Chemistry** | |
| **Electrolytes** | Bicarbonate, calcium, chloride, phosphate, potassium, sodium |
| **Liver function tests** | Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin |
| **Renal function tests** | Blood urea/blood urea nitrogen, creatinine |
| **Other** | Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid |
| **Urinalysis** | Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells |
| **Other** | Lymphocyte T and B cell subset analyses (see Table 5). Regulatory T cells (revised per Amendment 04)<br>PBMCs (revised per Amendment 02)<br>Ig analyses (IgG, IgA, and IgM).<br>Viral screen (HCVAb [Hepatitis C] and HbsAg [Hepatitis B]).<br>Viral characterization (including HSV1, HSV2 and CMV, etc)<br>Serum pregnancy test (females of child bearing potential only)<br>Tuberculosis Interferon Gamma Release Assays<br>Tests for thyroid function (thyroid stimulating hormone, free triidothyronine and free thyroxine) and vitamin B12<br>Blood sample for storage for subsequent testing of immune status<br>Cerebrospinal fluid sampling |

Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials must also be repeated. (revised per Amendment 02)

CMV = cytomegalovirus, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV = herpes simplex virus, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PT = prothrombin time, PTT = partial thromboplastin time.

The 8 different surface markers (including but not limited to CD3, CD4, CD8, CD45, CD19, CD16, CD56, and CD14) and total lymphocyte counts will be measured in order to provide the lymphocyte subset data as shown in Table 5. In addition, Regulatory T cells will be measured. Current sponsor data supports the literature showing there is an age-related decline in lymphocyte subsets (see Appendix 5). These data have been used to revise the LLNs for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts to the population-adjusted LLNs of 396, 157, and 74 cells/µL, respectively) (revised per Amendments 02 and 04).

**Table 5 Lymphocyte Subtypes Inclusive in BD Trucount™**

| Cell Type | Cell Surface Markers |
|---|---|
| T lymphocytes | CD3 |
| T helper cells | CD3+, CD4 |
| Cytotoxic T cells | CD3+, CD8 |
| Mature B cells | CD3-, CD19 |
| Natural killer cells | CD3-, CD16, CD56 |
| Macrophages | CD14 |

(Table 5 revised per Amendment 04)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the case report form [CRF] Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

#### 9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [bpm], respiratory rate [per minute], body temperature [in centigrade], and weight [kg]) will be obtained at the visits designated in Table 6 and Table 7 by a validated method. Measurements of sitting BP and heart rate will be obtained. All BP measurements should be performed on the same arm, preferably by the same person.

#### 9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination will be performed at Screening as described in Section 9.5.1.2.1. At Baseline and during the Randomization Phase, routine physical examinations will take place as shown in Table 7. These examinations will include the cardiovascular system, respiratory system, and neurological system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 6 and Table 7. Twelve-lead standard ECGs will be recorded in triplicate (1 minute apart) after subjects have been resting

in the supine position for at least 5 minutes.

On any study day when ECG, vital signs, and blood samples are taken, these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.7 SAFETY MRI

Safety brain MRI assessments will be performed at the times shown in Table 6 and Table 7. Additional safety MRI scans can be performed at unscheduled visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Safety MRIs will be acquired using a standardized procedure that will include fluid-attenuated inversion recovery (FLAIR), gradient-echo, T1, and diffusion-weighted sequences to determine the presence of focal lesions including, but not limited to, evidence for ischemic and hemorrhagic stroke, subdural hematoma, neoplasm, arteriovenous malformation, micro and macrohemorrhages, superficial siderosis, lacunar infarcts, white matter abnormalities, and vasogenic edema. The imaging sequence for the Screening/safety MRI will include: T2 weighted anatomic MRI to rule out major white matter changes, cerebral infarction or other structural lesions, and a high-resolution 3D T1-weighted scan with isotropic voxels with volumes of 1 $mm^3$ or less. In addition, both FLAIR for the detection of vasogenic edema and T2 Gradient Recall Echo for the detection of microhemorrhages will be acquired. The 3D dataset will be reconstructed in transverse slices in Digital Imaging and Communications in Medicine format. The results of this MRI assessment will also be used as the Baseline Period MRI, against which changes after drug administration will be compared. Further details of the MRI protocol can be found in the Imaging Acquisition Guideline. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, and 18 and at the final Follow-Up Visit (Visit 20). (revised per Amendment 04) In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

At any time during the treatment period, subjects will be discontinued from study drug if they develop any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. All of these features must be reported as study specific AEs (or AEs of special interest). These subjects will undergo an ED Visit within 7 days after discontinuation and 4 Follow-Up Visits at 2, 4, 8 and 12 weeks after the last dose of treatment. (revised per Amendment 04) Subjects will also undertake an

Unscheduled Visit (with MRI) at approximately 30 days after the visit at which such MRI features were first identified. Additional visits may be arranged if clinically indicated in the opinion of the investigator, and may occur later than 12 weeks after the final dose of study drug.

#### 9.5.1.5.8 DERMATOLOGICAL ASSESSMENT

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at the times shown in Table 6 and Table 7. These assessments will specifically include evaluation of any areas of depigmentation or any rash.

In addition, subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregiver or informants will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or infection, and the investigator will be required to review such AEs as soon as possible and consider an unscheduled physical and dermatological evaluation. Detailed characteristics of any skin rashes will be captured in the clinical database. Physical examination may be undertaken where indicated. Treatment-emergent abnormal dermatological findings should be reported as AEs.

#### 9.5.1.5.9 NEUROLOGICAL EXAMINATION

Neurological examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations as shown in Table 6 and Table 7. Details of these examinations will be captured in an eCRF. The neurological examinations will monitor for new symptoms and signs which will then alert the investigator to consider new CNS pathology (especially slowly-evolving neurological conditions that may not lead to prominent symptoms). Examples of neurological signs that may indicate new CNS pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. In such a situation, the investigator should consider (but not limited to) demyelination in the differential diagnoses, and should discuss with the sponsor's medical monitor further investigations or treatment, which will be decided case by case. Neurological examinations will also include the assessment of cranial nerve function, especially the olfactory nerve; the Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits to objectively test olfaction. Treatment-emergent abnormal neurological findings should be reported as AEs.

#### 9.5.1.5.10 PREGNANCY TEST

At Screening, females of childbearing potential will have a serum pregnancy test. At Baseline and during the Treatment Period, urine samples will be obtained from females of childbearing potential for pregnancy tests (see Table 7).

#### 9.5.1.5.11 COLUMBIA SUICIDE SEVERITY RATING SCALE

An assessment of suicidal ideation and behavior using the C-SSRS will be performed at the designed time points in Table 6 and Table 7. A "yes" answer to Type 4 or 5 suicidal ideation or a "yes" response to any suicidal behavior queries will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

#### 9.5.1.5.12 BIOMARKER SAMPLES

As noted in Section 9.5.1.4.2, CSF (for subjects who consent to CSF sample collection), blood, and DNA samples will be collected and may be used for exploratory biomarker analyses, as well as tested in the event that a subject develops AEs that warrant further investigation. (revised per Amendment 02)

#### 9.5.1.5.13 OPHTHALMIC EXAMINATIONS

An ophthalmic examination will be conducted at Baseline (unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available). An additional examination will be conducted, if the subject experiences visual disturbances during the course of the study or is medically indicated. The ophthalmic examinations should include fundoscopy to look at the optic disc, macula and the rest of the retina, as well as an assessment of visual acuity and visual fields.

### 9.5.2 Schedule of Procedures/Assessments

#### 9.5.2.1 Schedule of Procedures/Assessments

Table 6 presents the Schedule of Procedures/Assessments for the Prerandomization Phase. Screening assessments will be organized into 4 tiers (see below and Figure 2).

Table 7 presents the Schedule of Procedures/Assessments for the Randomization Phase.

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

| Phase | Prerandomization | |
|---|---|---|
| Period | Screening | Baseline |
| Visit | 1 | 2 |
| **Procedures/Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)** | | |
| Informed consent (subject and caregiver or informant) | X (Tier 1) | |
| Subject informed consent for CSF sample collection (voluntary)[a] | X | X |
| Demographics | X (Tier 1) | |
| Medical history[b] | X (Tier 1) | |
| Prior / concomitant medications[c] | X (Tier 1) | X |
| Vital signs including weight[d] | X (Tier 1) | X |
| Height | X (Tier 1) | |
| Complete physical examination | X (Tier 1) | |
| Routine physical examination | | X |
| CBB and ISLT[e] | X (Tier 1) | X |
| MMSE[e] | X (Tier 1) | X |
| CDR[e] | X (Tier 1) | X |
| FAQ[e] | X (Tier 1) | X |
| ADAS-cog$_{14}$[e] | | X |
| 15-item Geriatric Depression Scale | X (Tier 2) | |
| Modified Hachinski ischemic scale | X (Tier 2) | |
| C-SSRS | X (Tier 2) | X |
| 12-lead ECG[f] | X (Tier 2) | X |
| Blood and urine for clinical laboratory tests[g] | X (Tier 2) | X |
| Blood for lymphocyte subset analyses[h] | X (Tier 2) | X |
| Blood for Ig analyses[i] | X (Tier 2) | X |
| Blood for viral screen[j] | X (Tier 2) | |
| Blood for thyroid function tests[k] | X (Tier 2) | |
| Blood for vitamin B12 test | X (Tier 2) | |
| Test for previous TB exposure | X (Tier 2) | |
| Urine drug screen | X (Tier 2) | |
| Serum pregnancy test (females of childbearing potential only) | X (Tier 2) | |
| Urine pregnancy test (females of childbearing potential only) | | X |
| Safety and Volumetric MRI[l] | X (Tier 3) | |
| Amyloid PET scan[m] | X (Tier 4) | |
| Inclusion and Exclusion criteria | X (All tiers) | X |
| Adverse events | X (All tiers) | X |
| CSF sampling for PK, PD and storage[a] | | X |
| Blood sample for PK assessments[n] | | X |
| Blood sample for PD and exploratory biomarker assessments[o] | | X |
| Blood sample for pharmacogenomics | | X |
| Blood sample for storage for immune status[p] | | X |
| Blood sample for PBMC isolation | | X |
| Blood sample for viral characterization[q] | | X |
| Centralized dermatological assessment via photography[r] | | X |
| Neurological examinations[s] | | X |
| Ophthalmic assessment[t] | | X |

(Table revised per Amendments 02 and 04)

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

AChEI = acetylcholinesterase inhibitor, AD = Alzheimer's disease, ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CDR = Clinical Dementia Rating, CMV = cytomegalovirus, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), Ig = immunoglobulin, INR = International Normalized Ratio, ISLT = International Shopping List Task (immediate and delayed recall), LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetics, PET = positron emission tomography, PT = prothrombin time, PTT = partial thromboplastin time, TB = tuberculosis.

Note: Screening assessments/procedures have been organized into 4 distinct tiers. All assessments and procedures in each tier should be completed (see Figure 2), and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures, as long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. Similarly, all screening assessments and procedures must be completed, and eligibility to continue in the study confirmed, before any baseline assessments and procedures commence. Adverse events and eligibility against inclusion and exclusion criteria must be assessed at each stage within the Screening Visit and at the Baseline Visit. (revised per Amendment 01)

Note: All screening and baseline assessments are to be completed within 50 days, plus an additional window of up to 30 days if required (revised per Amendment 02). The interval between availability of the results of the last screening assessment (PET scan) and the first baseline (Visit 2) assessments should be as short as possible and ideally should not exceed 7 days. Visit 3 (Randomization) (see Table 7) should occur no more than 10 days after completion of the Baseline visit (Visit 2) and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion No.20 into account (revised per Amendment 02). Thus, the total Prerandomization Phase may be up to 60 days, plus an additional window of up to 30 days if required (revised per Amendment 02).

a: Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. For those subjects who do consent to CSF sample collection: CSF will be collected by LP after fasting (preferred), or at least 2 hours after the most recent meal. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 [or later postrandomization timepoint] and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. If the LP and cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. The CSF sample will be used for PK and PD assessments. A CSF sample will also be stored for testing in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). (revised per Amendments 01, 02, and 04)

b: To include: mild cognitive impairment and AD history; history of TB, vaccination history against and infections due to varicella zoster virus (chickenpox and herpes zoster or shingles); infections due to HSV1 (orolabial herpes or cold sores) and 2 (genital herpes). Medical history of infections to include: onset, duration, relapse frequency, severity, and treatments. For any active infection within the last 4 weeks prior to randomization, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)

c: Prior and concomitant medications include AChEIs and memantine, and other medications for cognitive decline.

d: Weight, respiratory rate, body temperature, and sitting blood pressure and heart rate will be obtained.

e: To be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). At the Screening Visit, the recommended order of assessments is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. At the Baseline Visit, the assessments are to be conducted in the following order: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). (revised per Amendment 02) At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

f: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

g: Clinical laboratory tests consist of hematology (including PT, PTT, and INR), clinical chemistry, and urinalysis.

h: Lymphocyte subsets will include but are not limited to the following cell surface marker assessments: CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cells), CD16/CD56 (natural killer cells) and CD14 (macrophages). Regulatory T cells will also be measured. Viability staining may also be employed. Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials, must also be repeated. (revised per Amendments 02 and 04)

i: Igs to be analyzed include IgG, IgA and IgM.

j: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

k: Thyroid function tests include thyroid stimulating hormone, free triidothyronine, and free thyroxine.

l: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images. MRI will be read by an approved central reader. Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session. (revised per Amendment 01)

m: PET scanning will be performed with a locally approved β-amyloid imaging agent, eg, Amyvid if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. The PET image will be centrally read for the purpose of determining eligibility for inclusion into the study. An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02)

n: The PK blood sample should be collected on the same day shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

o: The PD and exploratory biomarker blood sample should be collected shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

p: A blood sample will be collected at Baseline and stored. This sample may be used for exploratory biomarkers associated with study drug or disease, or in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

q: Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

r: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. See Section 9.5.1.5.8 for further details.

s: To be performed by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. Section 9.5.1.5.9 details what is included in the neurological examination. The Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits and serves as part of the neurological examination. (revised per Amendment 04)

t: An ophthalmic examination will be conducted at Visit 2 unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available. The ophthalmic examination should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields.

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| Phase | Randomization | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Period | Treatment | | | | | | | | | | | | | | | | | Follow-Up | | | | |
| Visit[a] | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | ED[b] | W2 | 19[c] | W8 | 20[c] | UNS Visit[d] |
| Day | 1 | 8 | 15 | 22 | 29 | 43 | 57 | 71 | 85 | 113 | 141 | 183 | 274 | 365 | 456 | 547 | | 561 | 575 | 589 | 631 | |
| Week | 1 | 2 | 3 | 4 | 5 | 7 | 9 | 11 | 13 | 17 | 21 | 27 | 40 | 53 | 66 | 79 | | 81 | 83 | 87 | 91 | |
| Weeks elapsed since first dose | 0 | 1 | 2 | 3 | 4 | 6 | 8 | 10 | 12 | 16 | 20 | 26 | 39 | 52 | 65 | 78 | | 80 | 82 | 86 | 90 | |
| Nominal months elapsed since first dose | 0 | | | | 1 | | 2 | | 3 | 4 | 5 | 6 | 9 | 12 | 15 | 18 | | | 19 | | 21 | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | | | |
| Routine physical examination | X | | | | X | | X | | X | | | X | X | X | X | X | X | | X | | X[e] | X |
| Inclusion and Exclusion criteria | X | | | | | | | | | | | | | | | | | | | | | |
| Vital signs[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X[e] | X |
| Respiratory rate | | | | | X | | X | | X | X | X | X | X | X | X | X | X | | X | | X[e] | X |
| Weight | | | | | | | | | X | | | X | X | X | X | X | X | | | | X | X |
| Centralized dermatological assessment via photography[g] | | | | | | | | | X | | | X | X | X | X | X | X | | | | X | X |
| Neurological examination[h] | | | | | | | | | | | | X | | X | | X | X | | X | | X | X |
| Ophthalmic examination[i] | | | | | | | | | | | | | | | | | | | | | | X |
| Concomitant medications[j] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | X |
| 12-lead ECG[k] | | | X | | X | | X | | X | | | X | | X | | X | X | | X | | X[e] | X |
| Clinical biochemistry and urinalysis | | | X | | X | | X | | X | | | X | X | X | X | X | X | | X | | X | X |
| Complete blood count | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[l] |
| Blood samples (lymphocyte subset analyses)[l] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[l] |
| Blood samples (Igs)[m] | | | | | X | | X | | X | | | X | | X | | X | X | | X | X | X | X |
| Blood samples (isolation of PBMCs) | | | X | | | | | | X | | | | | | | | | | | | X | |
| Urine pregnancy test (females of CBP only) | X[n] | | | | | | | | X | | | X | X | X | X | X | X | | X | | | X |
| Blood sample (storage for immune status)[o] | | | | | X | | | | X | | | X | | X | | X | X | | X | | X | X |
| CBB and ISLT[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | |
| MMSE[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | |
| CDR[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | |
| ADAS-cog$_{14}$[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | |
| FAQ[p] | | | | | | | | | X | | | X | X | X | X | X | X | | X | | X | |
| C-SSRS | | | | | X | | X | | X | | | X | X | X | X | X | X | | X | | X[e] | X |
| Safety and Volumetric MRI[q] | | | | | | | | | | | | X | | X | | X | X | | | | X | X |
| Amyloid PET[r] | | | | | | | | | | | | | | | | X | X | | | | | |
| Telephone contact[s] | | | X | | X | | | | X | | | X | | X | | X | X | | | | | X |
| Blood samples for PK[t] | | | X | | X | | | | X | | | X | | X | | X | X | | | | | X |

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| **Phase** | **Randomization** | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | | | | | **Follow-Up** | | | | |
| **Visit**[a] | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **ED**[b] | **W2** | **19**[c] | **W8** | **20**[c] | **UNS Visit**[d] |
| **Day** | **1** | **8** | **15** | **22** | **29** | **43** | **57** | **71** | **85** | **113** | **141** | **183** | **274** | **365** | **456** | **547** | | **561** | **575** | **589** | **631** | |
| **Week** | **1** | **2** | **3** | **4** | **5** | **7** | **9** | **11** | **13** | **17** | **21** | **27** | **40** | **53** | **66** | **79** | | **81** | **83** | **87** | **91** | |
| **Weeks elapsed since first dose** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **10** | **12** | **16** | **20** | **26** | **39** | **52** | **65** | **78** | | **80** | **82** | **86** | **90** | |
| **Nominal months elapsed since first dose** | **0** | | | | **1** | | **2** | | **3** | **4** | **5** | **6** | **9** | **12** | **15** | **18** | | | **19** | | **21** | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | | | |
| Blood samples for PD and exploratory biomarkers[u] | | | X | | X | | | | X | | | X | | X | | X | X | | X | | X | |
| CSF sampling for PK and PD[v] | | | | | X | | | | | | | | | | | X | X | | | | | X |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[l] |
| Sleep/dream questionnaire[w] | | | | | | | | | | | | | | | | | | | | | | X |
| Randomization | X | | | | | | | | | | | | | | | | | | | | | |
| Dispense study drug[x] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | | |

**Footnotes for Table 7**

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating scale, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), Ig = immunoglobulin, ISLT = International Shopping List Task, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, UNS = unscheduled, W2 = new Week 2 follow-up visit, W8 = new Week 8 follow-up visit. (revised per Amendment 04)

a: Visit 3 should be conducted no more than 10 days after completion of the Baseline visit (Visit 2) assessments and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion #20 into account. (revised per Amendment 02) A window of ±3 days will be permitted for Visit 4 to 14 inclusive. A window of ±10 days will be permitted for Visit 15 to 18 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since first dose" at subsequent visits.

b: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug (Visit W2, 19, W8, and Visit 20, respectively). Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie. at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB, and ISLT) will be conducted. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) after the Early Discontinuation Visit or within ± 8 days of Follow-Up Visit 19 of Visit 20). Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above. (revised per Amendment 04)

c: All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 4 post-treatment Follow-Up visits; 2, 4, 8, and 12 weeks after the last dose of study drug (Visits W2, 19, W8, and 20, respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the post-treatment Follow-Up period. (revised per Amendment 04)

d: Unscheduled visits may be conducted at any time that safety or safety MRI data indicate per protocol or as clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

e: Only if clinically significant abnormalities are found at Visit 19 and the investigator considers it necessary to repeat at Visit 20. Clinical biochemistry, urinalysis, CBC, lymphocyte subsets and Igs should always be performed at Visit 20, regardless of clinical significance at the previous Follow-Up visit. (revised per Amendments 02 and 04)

f: Measurements of body temperature and sitting blood pressure and heart rate will be obtained.

g: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. Additional UNS dermatological assessments should be conducted in response to any dermatological AEs of concern (eg, depigmentation, rash, herpetic lesion).

h: Examples of neurological signs that may indicate new central nervous system pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. The Brief Smell Identification Test (Sensonics Inc.) will be administered at the same visits and serves as part of the neurologic examination. (revised per Amendment 04)

i: If the subject experiences visual disturbances during the course of the study, the subject will be referred to a specialist for a further ophthalmic examination, which should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields

j: Please refer to Section 9.4.7, which details prohibited and permitted medications in the study and associated timeframes.

k: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

**Footnotes for Table 7**

l: Lymphocyte subsets will include but are not limited to the following cell surface marker assessments: CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [NK cells] and CD14 [macrophages]) and total lymphocytes. Regulatory T cells will also be measured. Viability staining may also be employed. Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a Complete Blood Count, with differentials, must also be performed along with assessment of AEs. (revised per Amendments 02 and 04)

m: Igs to be analyzed include IgG, IgA, and IgM.

n: An additional assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

o: Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops a TEAE that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

p: These assessments are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The order of assessments will be: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). At visits where the CDR or FAQ are conducted, the investigator will determine whether the informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

q: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images in MRI will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, 18, and 20. In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A volumetric MRI sequence will be collected in all subjects immediately following all safety MRI assessments. (revised per Amendment 01)

r: PET scanning will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks. A PET scan will only be performed at Visit 18 or ED if the subject has a valid Screening PET scan for the purposes of longitudinal analyses; subjects who were determined to be eligible for the study on the basis of an historical PET scan will not have a PET scan performed at Visit 18 or ED (revised per Amendment 02)

s: Site staff will contact the subject or the caregiver or informant the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the caregiver or informant, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

t: Two plasma PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visit 5, Visit 11, Visit 14, and Visit 16 and 4 to 8 hours postdose at Visit 7 and Visit 18 (or ED). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or ED) the PK blood sample should be collected shortly before or shortly after completing the LP. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected, followed by LP at approximately the same time as at previous visits. A second PK blood sample will be collected as close as possible to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

u: PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day. At Visits 5, 11, 14, and 16 the PD blood samples should be collected predose.

v: For subjects who consent to CSF sample collection: Postrandomization CSF sample collection is scheduled at Visit 7 (or later postrandomization timepoint) and Visit 18/ED. If a postrandomization CSF sample is collected later than Visit 7, time-matched plasma PK samples are also required (see Footnote t). All visits at which CSF samples are scheduled to be taken also include blood PK and PD assessments and so the subject will be dosed at the clinic on these days. The timing of the Baseline LP needs to be

**Footnotes for Table 7**

scheduled carefully such that subsequent LPs (Visit 7 [or later postrandomization timepoint] and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If the LP and the cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. . Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample will be approached to consider reconsenting to postrandomization CSF sample collection even if they are beyond Week 5 (Visit 7); however, subject reconsent to this procedure is optional for these subjects. (revised per Amendments 01, 02, and 04)

w: Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

x: The first dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time as determined by the PI or Safety Physician for postdose medical observation. (revised per Amendment 02)

#### 9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 6 and Table 7 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 4 tiers (see Table 6, Section 9.5.2, and Figure 2.

See Section 9.5 for a full description of the procedures and assessments to be performed during this study.

Table 8 presents the number of blood and CSF samples, and the total volume of blood and CSF that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety.

**Table 8 Summary of Blood and CSF Sample Volumes**

| Assessment | Total number of collection time points | Number of time points x volume per collection (mL whole blood or CSF) | | Total volume (mL whole blood or CSF) |
|---|---|---|---|---|
| | | Screening and Baseline Periods | Treatment and Follow-Up Periods | |
| **Blood** | | | | |
| Chemistry | 12 | 2 x 2 mL | 10 x 2 mL | 24 mL |
| Hematology | 20 | 2 x 5 mL | 18 x 5 mL | 100 mL |
| Lymphocyte subset analyses[a] | 20 | 2 x 4 mL | 18 x 4 mL | 80 mL |
| PBMC | 4 | 1 x 16 mL | 3 x 16 mL | 64 mL |
| IgA, IgM, IgG | 10 | 2 x 2 mL | 8 x 2 mL | 20 mL |
| PT, PTT for INR | 2 | 2 x 3 mL | None | 6 mL |
| Thyroid function tests (thyroid stimulating hormone, free triidothyronine and free thyroxine) | 1 | 1 x 3 mL | None | 3 mL |
| Viral screen (Hepatitis B and C) | 1 | 1 x 4 mL | None | 4 mL |
| Viral characterization | 1 | 1 x 4 mL | None | 4 mL |
| Vitamin B12 | 1 | 1 x 2 mL | None | 2 mL |
| Serum pregnancy test | 1 | 1 x 2 mL | None | 2 mL |
| Tuberculosis (interferon-gamma release assays) | 1 | 1 x 3 mL | None | 3 mL |
| Sample for immune status | 8 | 1 x 4 mL | 7 x 4 mL | 32 mL |
| PD sample | 9 | 1 x 4 mL | 8 x 4 mL | 36 mL |
| PK analysis | 7 | 1 x 3 mL | 6 x 6 mL | 39 mL |
| Pharmacogenetic sample | 1 | 1 x 3 mL | None | 3 mL |
| All blood samples, total volume whole blood collected | | 80 mL | 342 mL | 422 mL |
| **CSF (For subjects who consent to CSF sample collection) (revised per Amendment 02)** | | | | |
| PD and PK samples | 3 | 1 x 12 mL | 2 x 12 mL | 36 mL |

CSF = cerebrospinal fluid, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetic, PT = prothrombin time, PTT = partial thromboplastin time.

a: Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials must also be performed. Therefore, for each unscheduled or repeat test, an additional 9 mL will be collected (5 mL for hematology and 4 mL for lymphocyte subset analyses)

(Table 8 revised per Amendment 04)

### 9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include vital signs, clinical laboratory assessments, physical examinations, ECG measurements, and reports of AEs. MRI will be used to detect vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage and is a standard evaluation to ensure subject safety. The C-SSRS has been endorsed by the FDA as a measure of potential suicidality (Guidance for Industry Suicidality).

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, in addition to mitigating clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. Details are provided in Section 9.2.6.

### 9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

#### 9.5.4.1 Reporting of Serious Adverse Events

**All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.**

SAEs, regardless of causality assessment, must be collected up to 3 months after the last dose of study drug, ie, through to the final follow-up visit (Visit 20). (revised per Amendment 04) In subjects who discontinue study drug early, but continue with efficacy assessments, SAEs only need to be solicited up to 3 months after the last dose of study drug. However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

**For urgent safety issues**, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

#### 9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must discontinue study treatment.

#### 9.5.4.3 Reporting of Events Associated with Special Situations

#### 9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

| | |
|---|---|
| Overdose | Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose |
| Misuse | Intentional and inappropriate use of study drug not in accordance with the protocol |
| Abuse | Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects |
| Medication error | Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject |

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

#### 9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2) should always be considered serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

### 9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

#### 9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

#### 9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

### 9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue study drug or withdraw from the study at any time for any reason. All subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 2, 4, 8, and 12 weeks after the last dose of study drug (Visits W2, 19, W8, and Visit 20, respectively) (see Section 9.1.2.3). (revised per Amendment 04) See Table 7 for full details of the assessments to be performed at these visits. Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie, at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog14, FAQ, CBB and ISLT) will be conducted. Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above. Subjects who discontinue study drug early (as opposed to subjects whose dosing with study drug is temporarily suspended under Medical Monitor guidance) will not be permitted to restart study drug.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and will provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who withdraw prematurely from the study will be withdrawn for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for withdrawal from the study. Study disposition information will be collected on the Subject Disposition eCRF.

A subject removed from the study for any reason may not be replaced.

### 9.5.6 Abuse or Diversion of Study Drug

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF. (revised per Amendment 04)

### 9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

## 9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

### 9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all

clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

### 9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy assessments performed in this study.

## 9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, except for the Bayesian methods on the primary endpoint.

### 9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the statistical analysis plan, which will be finalized before the first interim efficacy analysis.

#### 9.7.1.1 Study Endpoints

See Section 9.2.3 for a discussion of the rationale for the selection and clinical relevance of the primary study endpoint. Further information on the derived ADCOMS is described in Section 9.5.1.3.1.

##### 9.7.1.1.1 PRIMARY ENDPOINT

- Change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects

#### 9.7.1.1.2 SECONDARY ENDPOINTS

Change from baseline in: (revised per Amendment 02)

- Total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- The derived ADCOMS at 18 months of treatment in mild to moderate AD subjects (revised per Amendment 01)

#### 9.7.1.1.3 EXPLORATORY ENDPOINTS

(revised per Amendments 01, 02, and 04)

Change from baseline in:

- The derived ADCOMS at 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
- Total hippocampal volume at 12 and 18 months of treatment in mild to moderate AD subjects as measured by vMRI
- CSF Aβ(1-x) and Aβ(1-42) after at least 4 weeks and at 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ in MCI/Prodromal and mild to moderate AD subjects
- CSF biomarkers of neurodegeneration (eg, tau and p-tau) at 18 months of treatment in MCI/Prodromal and mild moderate AD subjects
- Plasma and CSF amyloid, and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during post-treatment follow-up in MCI/Prodromal and mild moderate AD subjects
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months in MCI/Prodromal and mild to moderate AD subjects as measured by vMRI
- Brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- The population PK parameters of E2609 including the effect of intrinsic and extrinsic factors (including *NAT2* phenotype) in MCI/Prodromal and mild to moderate AD subjects

### 9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.

- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol (PP) Analysis Set is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

#### 9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: The number (percent) of randomized and treated subjects who completed the study and who withdrew from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and withdrew from the study. The primary reasons for discontinuation from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

Completion of Study Treatment: The number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for discontinuation from the study drug are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, inadequate therapeutic response, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

#### 9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, MMSE and FAQ; categorical variables include sex, age group (≤65 years, age >65 years), race, ethnicity, *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal AD or mild to moderate AD). (revised per Amendment 01)

#### 9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014 or higher). (revised per Amendment 04) The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up period will also be recorded.

#### 9.7.1.6 Efficacy Analyses

***The MCI/Prodromal Cohort***

The study in the MCI/Prodromal cohort is based on Bayesian adaptive design. Frequent interim analyses will be performed to assess the probability of early success and futility and to make early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis. Key definitions relevant to the Bayesian aspects of the adaptive design are given below.

**Study Definitions**

- **Maximum Effective Dose ($d_{Max}$):** The dose that achieves the greatest treatment effect.
- **$ED_{90}$:** The lowest dose that achieves at least 90% of the $d_{Max}$ treatment effect in the derived ADCOMS.
- **Early Success:** The study in the MCI/Prodromal cohort will meet early success criteria if the probability that the $ED_{90}$ at 18 months of treatment achieves 25% improvement over placebo is at least 80%. Early success is achieved before all MCI/Prodromal subjects complete 18 months of treatment and can only be determined after at least 200 MCI/Prodromal subjects have been randomized. If early success is declared before

full randomization, the randomization of new MCI/Prodromal subjects will stop but subjects already randomized into the study will receive the full 18 months of treatment (following confirmation from the Sponsor's Senior Management).

- **Futility:** The study in the MCI/Prodromal cohort will meet statistical futility criteria if the probability that the $ED_{90}$ is better than placebo by the clinically significant difference of 25% is less than 5% at 18 months of treatment. The statistical futility boundary is binding; if the statistical futility boundary is crossed the study will be considered to have failed.
- **Study Success:** The study in the MCI/Prodromal cohort will be considered a success if an $ED_{90}$ at 18 months treatment has at least an 80% probability of achieving 25% improvement over placebo at either an interim analysis or at the final analysis.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

All mild to moderate AD subjects will be included in the efficacy evaluations of the Mild to Moderate AD cohort. The analysis of the Mild to Moderate AD cohort is based on the group sequential design. Interim analyses in the Mild to Moderate AD cohort will only be performed after the MCI/Prodromal cohort crosses the early success boundary. The early efficacy signal based on the change from baseline of ADCOMS at 18 months is defined as crossing the interim-analysis boundaries for overwhelming efficacy in the mild to moderate AD population. The O'Brien-Fleming (OF) boundaries based on Lan-DeMets alpha spending function will be used to assess overwhelming efficacy. The corresponding OF boundaries based on *P* values will be 0.076, 0.0221, and 0.0423 for the first, second, and final analyses, respectively, according to 2 planned interim analyses at the 60% and 80% information fraction. (revised per Amendment 01)

#### 9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

***Primary analysis of primary endpoint***

The primary analysis will be based on MCI/Prodromal subjects from the FAS with the prespecified censoring rule applied. The primary endpoint is the change from baseline to 18 months in the derived ADCOMS. The dose-response of the primary endpoint is modelled with a first-order normal dynamic linear model, where Normal and Inverse-Gamma priors are used. The primary efficacy analysis will calculate the Bayesian posterior probability that the dose identified is the most likely $ED_{90}$ dose that achieves 25% improvement over the placebo arm. At each interim analysis and the final analysis, 2 Bayesian probabilities will be summarized for each active dose: the probability it is the $ED_{90}$ dose and the probability of achieving 25% improvement over the placebo arm.

For the clinical efficacy data (ie, derived ADCOMS, MMSE, CDR, ADAS-cog, CBB, ISLT, and FAQ) subjects will be censored at the time of initiation of treatment with AChEIs or memantine, if they were not on these medications at the time of Baseline cognitive

assessment (Visit 2), and will be censored at the time of dose adjustment of AChEIs or memantine if they were already on stable treatment with these medications at the time of Baseline cognitive assessment (Visit 2). The value of the primary endpoint for censored subjects will be imputed using data up to the censoring time and Bayesian longitudinal modeling.

***Sensitivity analysis of primary endpoint***

After unblinding, the primary endpoint will be analyzed using the Bayesian methods described above as well as conventional statistical methods. The following additional Bayesian analyses will be conducted as sensitivity analyses:

- The primary endpoint will be analyzed regardless of initiation of treatment, or dose adjustment, with AChEIs or memantine using the same Bayesian analysis method as primary analysis. This is an intent-to-treat analysis without any censoring.
- In case of early success, the primary analysis as well as the above sensitivity analyses will be repeated after all subjects have completed 18 months of treatment or have been lost to follow-up.

Statistical methods for the final conventional analyses will use a mixed-effects model with repeated measures (MMRM) on the change from baseline in the derived ADCOMS at 18 months. The model will include treatment groups, randomization stratification variables (the presence or absence of ongoing treatment with AChEIs or memantine or both, and *ApoE4* status), and baseline ADCOMS as covariates. Other covariates such as adjusted hippocampal volume will be studied. These analyses will be performed as sensitivity analyses on the FAS as well as the PP set and as such, no multiplicity adjustments will be made to account for the interim analyses. In case of early success, the conventional analyses will also be performed using the data collected before the interim analysis.

#### 9.7.1.6.2 SECONDARY EFFICACY ANALYSES

***The MCI/Prodromal Cohort***

An MMRM will be used to analyze the following secondary endpoint: (revised per Amendment 02)

- Change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI

Comparisons between each treatment group and placebo will be performed.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

The MMRM will be used to analyze the change from baseline of derived ADCOMS at 18 months in mild to moderate AD. If there is no treatment group-by-population interaction in the overall study, the MMRM analysis will include all subjects (MCI/Prodromal or mild to moderate AD) in the overall study. Otherwise, the MMRM analysis will only include subjects in the Mild to Moderate AD cohort. The comparison between placebo and active doses will be performed within mild to moderate AD subjects regardless of subjects included in the MMRM analysis. Dunnett's method will be used to control for multiplicity due to multiple comparisons.

#### 9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

(revised per Amendments 01, 02, and 04)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in the derived ADCOMS at 12 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in total hippocampal atrophy at 12 and 18 months in mild to moderate AD subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) after at least 4 weeks and at 18 months in MCI/Prodromal and mild to moderate AD subjects. Data from early discontinuations will also be included. (revised per Amendment 04)
- Change from baseline in the clinical assessments: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in plasma and CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during post-treatment follow-up in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and 18 months as measured by vMRI in MCI/Prodromal and mild to moderate AD subjects

A linear mixed-model will be used to analyze the following exploratory endpoints:

- Change from baseline in brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in CSF biomarkers of neurodegeneration (eg, tau, p-tau) at 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects

Data from early discontinuations will also be used as appropriate. Comparisons between each treatment group and placebo will be performed.

A linear mixed-model with repeated measures will be used to determine the relationship between the following endpoints:

- Change from baseline in the derived ADCOMS score and the change from baseline in biomarkers in CSF at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in the derived ADCOMS score and change from baseline in imaging biomarkers (hippocampal, whole brain, and total ventricular volumes) at 12 and 18 months in MCI/Prodromal and mild to moderate AD subjects

*ApoE* status for heterozygous and homozygous E4 carriers will be included in the model to assess the effect of *ApoE* status in this relationship.

#### 9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

##### 9.7.1.7.1 PHARMACOKINETIC ANALYSES

The PK Analysis Set will be used for E2609 concentration listings and for summaries of E2609 concentrations in plasma and CSF by dose and day. E2609 metabolite PK data may also be listed and summarized. (revised per Amendment 04)

A population PK approach will be used to characterize the plasma PK of E2609. For this approach, plasma PK data from this study will be pooled with relevant data from Phase 1 studies. As appropriate, the effect of covariates on the PK of E2609 will be evaluated. The PK model will be parameterized for oral clearance (CL/F) and apparent volume of distribution (Vz/F) for E2609. Derived exposure parameters such as steady state area under the concentration time curve (AUC) and average concentration ($C_{avg}$) of E2609 and other derived parameters will be calculated from the model using the individual estimates parameterized for oral clearance and dosing history. (revised per Amendment 04)

##### 9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Pharmacodynamic, PGx, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate statistical analysis plan. Please also refer to Appendix 3.

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). The percentage change from baseline in CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 variables (eg, activity and protein levels) after at least 4 weeks and at 18 months will be analyzed and presented graphically. Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status. (revised per Amendment 04)

Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels, amyloid load on PET, vMRI, and E2609 dose, plasma, and CSF exposure will be initially explored graphically and any emergent relationship will be explored through population PK/PD modeling. The PK/PD relationship between plasma PK parameters with other biomarkers may also be explored using similar methods. (revised per Amendment 04)

The relationship between plasma and CSF exposure to E2609 and the clinical efficacy scales (eg, MMSE, CDR) will be explored graphically. Additionally, the relationship between plasma exposures of E2609 and select lymphocyte parameters will be explored graphically, and any emergent relationship will be explored using population-based modeling methods. (revised per Amendment 04)

Exposure-safety analyses may also be conducted.

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. The genomic DNA samples may also be stored and used as described in Section 9.7.1.7.2. Details of PGx testing may be provided and reported separately.

#### 9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, and vital sign measurements will be summarized by treatment group using descriptive statistics.

#### 9.7.1.8.1 EXTENT OF EXPOSURE

The extent of exposure to study drug will be summarized as cumulative extent of exposure in 3-month intervals. The number and percent of subjects will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics in 3-month intervals. The number and percent of subjects will be presented by treatment group.

#### 9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 17.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and preferred term. A subject will be counted only once within an SOC and preferred term, even if the subject experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and preferred term. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

Adverse events will be summarized by the following subgroups: *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal or mild to moderate AD). (revised per Amendment 01)

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

#### 9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

Lymphocyte subsets measured (including but not limited to CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages] and regulatory T cells) will be summarized in the same manner as other

laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose.

Serum IgG, IgM, and IgA will be measured and summarized in the same manner as other laboratory parameters.

#### 9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

#### 9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to the end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 msec
- QTc interval >480 msec
- QTc interval >500 msec

Change from baseline in QTc interval:

- QTc interval increases from baseline >30 msec
- QTc interval increases from baseline >60 msec

#### 9.7.1.8.6 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog$_{14}$, MMSE, CDR, and CBB (Section 9.7.1.6).

## 9.7.2 Determination of Sample Size

### 9.7.2.1 Sample Size Rationale in the MCI/Prodromal Cohort

Primary endpoint – derived ADCOMS

The sample size and design characteristics to test the hypothesis for the primary objective based on the primary endpoint, change from baseline of the derived ADCOMS at 18 months, were determined by means of simulations. Extensive study simulations have shown that a total of 500 subjects will be sufficient to demonstrate that the most likely $ED_{90}$ dose achieves a 25% improvement over placebo with a probability of at least 80% in the interim and final analyses. There is at least a 90% probability of study success for the dose response scenarios where treatment was considered to have a clinically meaningful treatment effect. Simulations have also shown that if there is no obvious dose effect, the probability of falsely claiming superiority to placebo is at most 5%.

For each of the 4 treatment groups (3 active doses and placebo) the final number of subjects per group will differ depending on the observed interim treatment responses. The simulation plan will be an appendix to the statistical analysis plan and will present further details.

vMRI

The null hypothesis is that there is no difference between active dose and placebo. There are 3 null hypotheses corresponding to 3 active doses. The alternative hypothesis is that at least 1 null hypothesis is false (1-sided). The null hypotheses will be tested using Dunnett's method with 1-sided alpha of 0.05. The statistical power was estimated through simulation for a moderate dose-response assumption that the percent reduction in change from baseline of total hippocampal volume compared with placebo would be 15%, 20%, and 25% corresponding to the 3 doses, respectively. The estimated power for the actual planned study sample size is 78% at 18 months assuming an attrition rate of 20% at 18 months. Under a stronger dose-response assumption (ie, the percent reduction in change from baseline of total hippocampal volume compared with placebo is twice as much as that in the moderate dose-response assumption), the estimated power is at least 99% at 18 months.

Amyloid PET

The null and alternative hypotheses and the statistical test are the same as those for vMRI. To estimate the sample size for the amyloid PET imaging subgroup at 18 months, a common SD of the change from baseline was estimated at 0.33 and a reasonable mean difference between treatment and placebo was estimated as 0.25 (standardized uptake value ratio [SUVR]). Assuming a moderate dose-response, the best dose would achieve a difference of 0.25 (SUVR) and the middle and low doses would achieve a difference of 0.2 and 0.15 (SUVR), respectively; this would require a total of 100 subjects from all 4 arms at 18 months to achieve 80% power.

#### 9.7.2.2 Sample Size Rationale for the Mild to Moderate AD Cohort (revised per Amendment 01)

ADCOMS at Month 18

The null hypothesis is that there is no difference between active dose and placebo. There are 2 null hypotheses corresponding to 2 active doses. The alternative hypothesis is that at least 1 null hypothesis is false. The null hypotheses will be tested using Dunnett's test with 2-sided alpha of 0.05 as described for the Mild to Moderate AD cohort in Section 9.7.1.6.2. The statistical power was estimated through simulation for the dose-response assumption that the percent reduction in change from baseline of ADCOMS at 18 months compared with placebo would be 33% and 50% corresponding to the 2 doses, respectively. The estimated power for the actual planned 200 mild to moderate AD subjects is approximately 80% assuming a 2-sided alpha of 0.05. (revised per Amendment 01)

### 9.7.3 Interim Analysis

In order to make decisions about the remainder of the study as well as the full E2609 clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. Investigators, other clinical site staff, subjects and caregivers/informants will remain blinded to study treatment. (revised per Amendment 03)

An interim safety analysis will also be conducted when the Stage A subjects have completed 12 weeks of treatment (or discontinue study drug early) in Stage A. (revised per Amendments 01, 03, and 04)

***The MCI/Prodromal Cohort***

The Bayesian interim analyses and response adaptive randomization will be conducted by an unblinded external independent analysis group in accordance with the protocol. Oversight of the Bayesian interim analyses and response adaptive randomization will be conducted by an independent unblinded committee that has expertise with Bayesian adaptive design in clinical studies to ensure that the response adaptive randomization process and interim analyses

perform as expected. The analysis group will provide the interim analysis outcomes to the committee at each interim analysis. The committee will ensure the integrity of the interim analysis and response adaptive randomization process through review of efficacy data. In addition, the committee will act in an independent advisory capacity to monitor the Bayesian interim analysis outcomes according to the early success and futility boundaries prespecified in the protocol. The committee will not be charged with any subject safety issues; this will remain the responsibility of the DSMB.

If the predefined early success criteria are met during the recruitment period, further recruitment and enrollment of MCI/Prodromal subjects into the study will stop (following confirmation from the Sponsor's Senior Management) and all currently randomized subjects will complete the full 18 months of treatment. No further interim analyses will be conducted after achieving early success.

If the predefined threshold for futility is reached, no additional subjects will be randomized into the study and the treatment of subjects already randomized into the study will stop and the study will be declared as "failed". All subjects will be monitored for safety for 3 months following their last dose.

If neither early success nor futility is reached and the study reaches full randomization, all subjects will complete 18 months of treatment. Interim efficacy analyses will be conducted every 3 months after full randomization is reached to assess futility and early success until all subjects complete 18 months of treatment. After full randomization, all study subjects will stop treatment only in the event of futility.

The DSMB will continue to monitor the safety aspects of the study throughout Stage A and Stage B. Details will be provided in the DSMB Charter. The study may be stopped for safety at any time.

The first Bayesian adaptive interim analysis will be conducted when 100 MCI/Prodromal subjects have been randomized into the study (ie, including MCI/Prodromal subjects from Stage A and Stage B). (revised per Amendment 01) Further interim efficacy analyses will be conducted after each additional 50 MCI/Prodromal subjects have been randomized, to a maximum of 500 MCI/Prodromal subjects (ie, at 100, 150, 200, 250, 300, 350, 400, 450, and 500 subjects randomized). If the study reaches full randomization, additional interim analyses will be conducted every 3 months until all subjects complete 18 months of treatment. The study will be monitored for futility at each interim analysis. Starting at the interim analysis for 200 subjects, the study will be monitored for success at each interim analysis. Each interim analysis will be conducted on data for the derived ADCOMS.

In addition, at each interim efficacy analysis, response adaptive randomization will be used to update the allocation of new subjects between placebo and active doses according to a predefined automated algorithm.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

A group sequential design will be used for the Mild to Moderate AD cohort. (revised per Amendment 01) This design includes 3 looks, 2 interim looks (when 60% and 80% information fractions are achieved) and 1 final look. The information fraction is the number of assessments in all treatment arms divided by the total number of expected assessments. Interim analyses will be performed after the MCI/Prodromal cohort crosses the early success boundary. The corresponding efficacy boundaries will be 0.076, 0.022, and 0.0423 for the first, second, and final analyses, respectively. If the actual information fraction during the interim analyses is different from 60% or 80% at the interim, the efficacy boundaries will be adjusted based on the actual information fraction.

If early success in the MCI/Prodromal cohort is not achieved before the final analysis that is performed when all subjects have completed 18 months treatment, then only a final analysis will be performed in mild to moderate AD subjects. In the event of futility in the MCI/Prodromal cohort, an analysis will be performed for the Mild to Moderate AD cohort based on the data for mild to moderate AD subjects available at that time. (revised per Amendment 01)

Randomization into the Mild to Moderate AD cohort will remain at a fixed schedule throughout Stage B. (revised per Amendment 01)

The interim analyses in the Mild to Moderate AD cohort will be conducted by an independent analysis group. (revised per Amendment 01)

### 9.7.4 Other Statistical/Analytical Issues

**Adaptive Randomization in the MCI/Prodromal Cohort**

Randomization to placebo or 1 of 3 dose groups of E2609 will be fixed for the first 100 MCI/Prodromal subjects randomized in the study (1:1:1:1; placebo to each of the 3 active doses for the first 100 MCI/Prodromal subjects randomized, including those randomized from both Stage A and Stage B). Thereafter, randomization probabilities to each treatment group will be updated at each interim analysis, such that the randomization probability will be increased for the placebo group and dosage groups that represent the potential target dose ($ED_{90}$), and simultaneously decreased for other active arms. (revised per Amendment 01)

**Randomization in the Mild to Moderate AD Cohort** (revised per Amendment 01)

In Stage A, the mild to moderate AD subjects will be randomized to placebo or 1 of 3 E2609 dose groups (5, 15, and 50 mg of E2609) at a 1:1:1:1 ratio, while in Stage B, the mild to moderate AD subjects will be randomized to placebo or 1 of 2 E2609 dose groups (15 and 50 mg E2609) at a 1:1:1 ratio. (revised per Amendment 01)

**Stratification** (revised per Amendment 01)

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

### 9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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(revised per Amendment 01)

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# 11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

## 11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

## 11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

## 11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

## 11.4 Recording of Data

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document, except when a section of the eCRF itself is used as the source document. Any correction to entries made on the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each eCRF. The investigator will report the eCRFs to the sponsor and retain a copy of the eCRFs.

## 11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents.

## 11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

## 11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

## 11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

## 11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

## 11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or CTA executed between the institution/investigator and the sponsor/CRO.

## 11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

## 11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

# 12 APPENDICES

## Appendix 1 Sponsor's Grading for Laboratory Values

(revised per Amendment 01)

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **BLOOD/BONE MARROW** | | | | |
| Hemoglobin (conversion from g/dL×0.6206) | **Female** (ULN=15.9 g/dL)<br><11.1 – 10.0 g/dL<br><111 – 100 g/L<br><6.9 – 6.2 mmol/L<br>**Male** (ULN=17.7 g/dL)<br><12.6 – 10.0 g/dL<br><126 – 100 g/L<br><7.8 – 6.2 mmol/L | <10.0 – 8.0 g/dL<br><100 – 80 g/L<br><6.2 – 4.9 mmol/L | <8.0 g/dL<br><80 g/L<br><4.9 mmol/L;<br>transfusion indicated | life-threatening consequences; urgent intervention indicated |
| Leukocytes (total white blood cell) | <3.40 – 3.0×$10^9$/L<br><3.40 $10^3$/uL – 3000/$mm^3$<br>(ULN=10.80 $10^3$/μL) | <3.0 – 2.0×$10^9$/L<br><3000 – 2000/$mm^3$ | <2.0 – 1.0×$10^9$/L<br><2000 – 1000/$mm^3$ | <1.0×$10^9$/L<br><1000/$mm^3$ |
| Lymphocytes | not applicable | <700 – 500/$mm^3$<br><0.7 – 0.5×$10^9$/L | <500 – 200/$mm^3$<br><0.5 – 0.2×$10^9$/L | <200/$mm^3$<br><0.2×$10^9$/L |
| Neutrophils | not applicable | <1.4 – 1.0×$10^9$/L<br><1400 – 1000/$mm^3$ | <1.0 – 0.5×$10^9$/L<br><1000 – 500/$mm^3$ | <0.5×$10^9$/L<br><500/$mm^3$ |
| Platelets | <155 – 75.0×$10^9$/L<br><155 $10^3$/uL – 75,000/$mm^3$<br>(ULN=379 $10^3$/μL) | <75.0 – 50.0×$10^9$/L<br><75,000 – 50,000/$mm^3$ | <50.0 – 25.0×$10^9$/L<br><50,000 – 25,000/$mm^3$ | <25.0×$10^9$/L<br><25,000/$mm^3$ |
| **METABOLIC/LABORATORY** | | | | |
| Albumin, serum- low (hypoalbuminemia) | **2 - 59 years** (ULN=5.5 g/dL)<br><3.5 – 3 g/dL<br><35 – 30 g/L<br>**59 -69 years** (LLN-ULN)<br><3.6 g/dL – 3 g/dL<br>**69 -79 years** (LLN-ULN)<br><3.5 g/dL – 3g/dL<br>**79 -89 years** (LLN-ULN)<br><3.5g/dL – 3g/dL | <3 – 2 g/dL<br><30 – 20 g/L | <2 g/dL<br><20 g/L | life-threatening consequences; urgent intervention indicated |
| Alkaline phosphatase | **Female:**<br>**18 -19 years**<br>>101 – 3.0×101<br>**19 -61 years**<br>ULN=107<br>**61 -71 years**<br>ULN=112<br>**71 -150 years**<br>ULN=108<br>**Male**<br>**18 -19 years**<br>>127 – 3.0×127<br>**19 -61 years**<br>ULN=102<br>**61 -71 years**<br>ULN=103<br>**71 -150 years**<br>ULN=105 | >3.0 – 5.0×ULN<br>See previous column for ULN values | >5.0 – 20.0×ULN<br>See previous column for ULN values | >20.0×ULN<br>See previous column for ULN values |
| Alanine aminotransferase | **Female:**<br>>32 – 3.0×32 | **Female:**<br>>3.0 – 5.0×32 | **Female:**<br>>5.0 – 20.0×32 | **Female:**<br>>20.0×32 |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| | **Male:**<br>>44 – 3.0 x 44 | **Male**<br>>3.0 – 5.0×44 | **Male:**<br>>5.0 – 20.0×44 | **Male:**<br>>20.0×44 |
| Aspartate aminotransferase | >40 – 3.0×40 | >3.0 – 5.0×40 | >5.0 – 20.0×40 | >20.0×40 |
| Bilirubin (hyperbilirubinemia) | >1.2 – 1.5×1.2 | >1.5 – 3.0×1.2 | >3.0 – 10.0×1.2 | >10.0×1.2 |
| Calcium, serum-low (hypocalcemia) (conversion to mmol×0.25) | <8.5 – 8.0 mg/dL<br><2.13 – 2.0 mmol/L | <8.0 – 7.0 mg/dL<br><2.0 – 1.75 mmol/L | <7.0 – 6.0 mg/dL<br><1.75 – 1.5 mmol/L | <6.0 mg/dL<br><1.5 mmol/L |
| Calcium, serum-high (hypercalcemia) | >10.6 – 11.5 mg/dL<br>>2.65 – 2.9 mmol/L | >11.5 – 12.5 mg/dL<br>>2.9 – 3.1 mmol/L | >12.5 – 13.5 mg/dL<br>>3.1 – 3.4 mmol/L | >13.5 mg/dL<br>>3.4 mmol/L |
| Cholesterol, serum-high (hypercholesterolemia) (conversion to mmol/L ×0.02586) | **0 -19 years**<br>>169 – 300 mg/dL<br>>4.37 – 7.75 mmol/L<br>**19 -150 years**<br>>199 – 300 mg/dL<br>>5.15 – 7.75 mmol/L | >300 – 400 mg/dL<br>>7.75 – 10.34 mmol/L | >400 – 500 mg/dL<br>>10.34 – 12.92 mmol/L | >500 mg/dL<br>>12.92 mmol/L |
| Creatinine | **Female**<br>>1.00 mg/dL – 1.5×1.00<br>**Male**<br>>1.27 mg/dL – 1.5×1.27 | **Female**<br>>1.5 – 3.0×1.00<br>**Male**<br>>1.5 mg/dL – 3.0×1.27 | **Female**<br>>3.0 – 6.0×1.00<br>**Male**<br>>3.0 mg/dL – 6.0 ×1.27 | **Female**<br>>6.0×1.00<br>**Male**<br>>6.0×1.27 |
| Gamma glutamyl transpeptidase | **Female**<br>>60 IU/L – 3.0×60<br>**Male**<br>>65 IU/L – 3.0×65 | **Female**<br>>3.0 – 5.0×60<br>**Male**<br>>3.0 – 5.0×65 | **Female**<br>>5.0 – 20.0×60<br>**Male**<br>>5.0 – 20.0×65 | **Female**<br>>20.0×60<br>**Male**<br>>20.0×65 |
| Glucose, serum-high (hyperglycemia) (conversion to mmol/L ×0.0555) | **Fasting glucose value**<br>>99 – 160 mg/dL<br>>5.5 – 8.9 mmol/L | **Fasting glucose value**<br>>160 – 250 mg/dL<br>>8.9 – 13.9 mmol/L | >250 – 500 mg/dL;<br>>13.9 – 27.8 mmol/L;<br>hospitalization indicated | >500 mg/dL;<br>>27.8 mmol/L;<br>life-threatening consequences |
| Glucose, serum-low (hypoglycemia) | <65 – 55 mg/dL<br><3.6 – 3.0 mmol/L | <55 – 40 mg/dL<br><3.0 – 2.2 mmol/L | <40 – 30 mg/dL<br><2.2 – 1.7 mmol/L | <30 mg/dL<br><1.7 mmol/L<br>life-threatening consequences;<br>seizures |
| Phosphate, serum-low (hypophosphatemia) (conversion to mmol/L ×0.323) | not applicable | <2.5 – 2.0 mg/dL<br><0.8 – 0.6 mmol/L | <2.0 – 1.0 mg/dL<br><0.6 – 0.3 mmol/L | <1.0 mg/dL<br><0.3 mmol/L<br>life-threatening consequences |
| Potassium, serum-high (hyperkalemia) | not applicable | >5.5 – 6.0 mmol/L | >6.0 – 7.0 mmol/L<br>hospitalization indicated | >7.0 mmol/L<br>life-threatening consequences |
| Potassium, serum-low (hypokalemia) | <3.5 mEq/L – 3.0 mmol/L | <LLN – 3.0 mmol/L;<br>symptomatic; intervention indicated | <3.0 – 2.5 mmol/L<br>hospitalization indicated | <2.5 mmol/L<br>life-threatening consequences |
| Sodium, serum-high (hypernatremia) | >144 mEq/L – 150 mmol/L | >150 – 155 mmol/L | >155 – 160 mmol/L<br>hospitalization indicated | >160 mmol/L<br>life-threatening consequences |
| Sodium, serum-low (hyponatremia) | <134 mEq/L – 130 mmol/L | Not applicable | <130 – 120 mmol/L | <120 mmol/L<br>life-threatening consequences |
| Triglyceride, serum-high (hypertriglyceridemia) | 150 – 300 mg/dL<br>1.71 – 3.42 mmol/L | >300 – 500 mg/dL<br>>3.42 – 5.7 mmol/L | >500 – 1000 mg/dL<br>>5.7 – 11.4 mmol/L | >1000 mg/dL<br>>11.4 mmol/L<br>life-threatening consequences |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Uric acid, serum-high (hyperuricemia) | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | Not applicable | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | >10 mg/dL<br>>0.59 mmol/L<br>life-threatening consequences |

LLN = lower limit of normal, ULN = upper limit of normal.

# Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1 through Listing 5. Medications permitted with restrictions are listed in Listing 6 through Listing 8. (revised per Amendment 04) **These may not be all-inclusive listings.** Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-202 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 8 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

## Prohibited Prior/Concomitant Medications

### Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Prohibited from 14 days (or 5 half-lives, whichever is longer) before Randomization until after the last treatment visit** | | |
| **Anti-arrhythmic/ abnormal heart rhythm** | | |
| Amiodarone | Cordarone; Pacerone | Incidence in females greater than males, Torsades de Pointes risk regarded as low |
| Disopyramide | Norpace | Incidence in females greater than males |
| Dofetillide | Tikosyn | |
| Ibutilide | Corvert | Incidence in females greater than males |
| Procainamide | Pronestyl; Procan | |
| Quinidine | Cardioquin; Quinaglute | Incidence in females greater than males |
| Sotalol | Betapace | Incidence in females greater than males |
| **Antihistamine/ allergic rhinitis** | | |
| Astemizole | Hismanal | No longer available in United States |
| Terfenadine | Seldane | No longer available in United States |
| **Anti-anginal/ heart pain** | | |
| Bepridil | Vascor | Incidence in females greater than males |
| **Antibiotic/ bacterial infection** | | |
| Clarithromycin | Biaxin | |
| Moxifloxacin | Avelox | |
| Sparfloxadin | Zagam | |
| **Listing 1 continued** | | |
| **Antimalarial/ malaria infection** | | |
| Chloroquine | Aralen | |
| Halofantrine | Halfan | Incidence in females greater than males |
| **Antipsychotic/ anti-emetic/ schizophrenia/ nausea** | | |
| Chloropromazine | Thorazine | |
| **Gastrointestinal stimulant/ heartburn** | | |
| Cisapride | Propulsid | |

## Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Antinausea/ nausea** | | |
| Domperidone | Motillum | Not available in the United States |
| **Sedative; antinausea/ anesthesia adjunct, nausea** | | |
| Droperidol | Inapsine | |
| **Antibiotic; gastrointestinal stimulant/ bacterial infection; increase gastrointestinal motility** | | |
| Erythromycin | Erythrocin; E.E.S. | Incidence in females greater than males |
| **Antipsychotic/ schizophrenia** | | |
| Haloperidol | Haldol | When given intravenously or at higher than recommended doses, risk of sudden death, QT prolongation, and torsades increases |
| Mesoridazine | Serentil | |
| Thioridazine | Mellaril | |
| **Opiate agonist/ pain control, narcotic dependence** | | |
| Levomethadyl | Orlaam | |
| Methadone | Methadose; Dolophine | Incidence in females greater than males |
| **Anti-infective/ pneumocystis pneumonia** | | |
| Pentamidine | Pentam; NebuPent | Incidence in females greater than males |
| **Antipsychotic/ Tourette's tics** | | |
| Pimozide | Orap | Incidence in females greater than males |
| **Antilipemic/ hypercholesterolemia** | | |
| Probucol | Lorelco | No longer available in United States |
| **Anticancer** | | |
| Arsenic trioxide | Trisenox | Used for leukemia |
| Vandetanib | Zactima | Used for thyroid cancer |

Note: This list is not exhaustive.

QTc = Corrected QT interval.

## Listing 2 Prohibited Medications Within 5 Half-lives or 60 days, Whichever is Longer, Before Randomization and Until after the Last Treatment Visit

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Systemic Immunosuppressants[a,b] and Immunomodulatory therapy** | |
| Azathioprine | Azasan, Imur |
| Ciclosporine | Gengraf, Neoral |
| Dexamethasone | Decadron, Dexasone, Diodex, Hexadrol, Maxidex |
| Fingolimod | Gilenya |
| Methotrexate | Trexall |
| Methylprednisolone | Medrol, Meprolone |
| Mycophenolate | CellCept, Myfortic |
| Prednisolone | Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS |

Note: This list is not exhaustive.

a: Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

b: During the treatment period of the study, short term (not more than 14 days) use of steroids up to the equivalent of prednisolone 40 mg OD is permitted after discussion with the Medical Monitor. Dosing with study drug should be suspended from the time steroid treatment is started. Complete blood count and lymphocyte subsets should be determined prior to starting steroid treatment and continue to be monitored weekly. Study drug may be resumed after discussion with the Medical Monitor when the following conditions are met: (1) treatment with steroids has been completed for at least 1 week; (2) total lymphocytes not <LLN; (3) no lymphocyte subsets are below the discontinuation threshold; (4) the investigator considers that the medical condition which required treatment with steroids has improved or resolved. Weekly testing of lymphocyte subset counts and CBC with differentials is required for 4 weeks following resumption of study drug administration. (revised per Amendment 04)

## Listing 3 Prohibited Medications Within 6 Months Before Randomization

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Immunoglobulin therapy** | |
| Adalimumab | Humira |
| Bevacizumab | Avastin |
| Efalizumab | Raptiva |
| Etanercept | Enbrel |
| Immune globulin IV, IVIG, IGIV | Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S |
| Infliximab | Remicade |
| Omalizumab | Xolair |
| Ranibizumab | Lucentis |
| Other monoclonal antibodies not listed here | |

Note: This list is not exhaustive.

### Listing 4 Prohibited Live Vaccines Within 3 Months Before Randomization Until after the Last Treatment Visit (this does not apply to non-live/inactivated vaccines)

| **Bacterial vaccines** | **Viral vaccines** |
|---|---|
| Bacillus Calmette-Guérin vaccine against tuberculosis | Measles vaccination |
| Cholera vaccination (oral) | Rubella vaccination |
| | Oral polio vaccination (Sabin) |
| | Yellow fever vaccination |
| | Varicella (chickenpox) vaccination |
| | Rotavirus vaccination |
| | Japanese encephalitis vaccination |
| | Live attenuated influenza vaccine (FluMist, Fluenz) |
| Typhoid vaccination (oral) | Mumps vaccination |

Note: This list is not exhaustive

## Listing 5 Strong CYP3A4 Inhibitors Prohibited Within 5 Half-Lives or 14 Days (Whichever Is Longer) Before Randomization Until After the Last Treatment Visit

| Generic name | Brand name(s) |
|---|---|
| boceprevir | Victrelis |
| clarithromycin | Clarithromycin, clarithromycin extended release, Prevpac |
| cobicistat | Tybost, Stribild, |
| conivaptan | Vaprisol |
| danoprevir | |
| elvitegravir | Vitekta, Stribild |
| indinavir | Crixivan |
| itraconazole | Sporanoz, Onmel |
| ketoconazole | Xolegel, Nizoral, Ketodan |
| lopinavir | Kaletra |
| nefazodone | Serzone |
| nelfinavir | Viracept |
| posaconazole | Noxafil |
| ritonavir | Norvir, Kaletra |
| saquinavir | Invirase, Fortovase |
| telaprevir | Incivek |
| telithromycin | Ketek |
| tipranavir | Aptivus |
| troleandomycin | Triocetin |
| voriconazole | Vfend, Voriconazole |

Note: This list is not exhaustive

## Permitted Prior/Concomitant Medications

### Listing 6 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Baseline Cognitive Assessments at Visit 2 and Remain on the Same Stable Dose from Baseline to Final Follow-Up Visit

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Cognitive Enhancers** | |
| Donepezil | Aricept |
| Galantamine | Reminyl |
| Memantine | Namenda |
| Rivastigmine | Exelon |

Note: This list is not exhaustive.

## Listing 7 Permitted Medications Used on PRN Basis Which are Not to be Used Within 72 Hours before Cognitive Testing

| **Generic name** | **Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™)** |
|---|---|
| **Opiates** | |
| Morphine | Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol |
| **Opiate Agonists** | |
| Codeine | Codeine |
| Fentanyl | Actiq, Duragesic, Fentora, Onsolis, Sublimaze |
| Meperidine | Demerol, Meperitab |
| Oxycodone | Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol |
| Other opioids or opioid agonists which are used on PRN basis | |
| **Benzodiazepines and sedatives** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Amitriptyline | (various) |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Dothiepin | (various) |
| Estazolam | ProSom |
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |
| Lorazepam | Ativan |
| Midazolam | Versed |
| Olanzapine | Zyprexa |
| Promethazine | Phenergan; others |
| Ramelteon | Rozerem |
| Risperidone | Risperdal |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zolpidem | Ambien; others |
| Zopiclone | (various) |
| Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives | |

Note: This list is not exhaustive

## Listing 7 Permitted Medications Used on PRN Basis Which are Not to be Used Within 72 Hours before Cognitive Testing

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|

PRN = Pro re nata

## Listing 8 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| If to be used on a PRN basis see Listing 7. If to be used chronically, subjects must be on a stable dose for ≥4 weeks before Baseline. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks. | |
| **Antidepressants** | |
| Amitriptyline hydrochloride | Elavil |
| Amoxapine | Amoxapine |
| Bupropion | Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin |
| Citalopram | Celexa |
| Clomipramine hydrochloride | Anafranil |
| Desipramine hydrochloride | Norpramin |
| Desvenlafaxine | Pristiq |
| Doxepin hydrochloride | Prudoxin, Silenor, Sinequan, Zonalon |
| Duloxetine | Cymbalta |
| Escitalopram | Lexapro |
| Fluoxetine | Prozac, Sarafem, Selfemra |
| Fluvoxamine | Luvox |
| Imipramine hydrochloride | Tofranil |
| Isocarboxazid | Marplan |
| Maprotiline hydrochloride | Ludiomil |
| Mirtazapine | Remeron Soltab |
| Nortriptyline hydrochloride | Aventyl, Pamelor |
| Paroxetine | Paxil, Pexeva |
| Phenelzine | Nardil |
| Protriptyline hydrochloride | Vivactil |
| Rasagiline | Azilect |
| Selegiline | EMSAM |
| Sertraline | Sertaraline, Zoloft |
| Tranylcypromine | Parnate |
| Trazodone hydrochloride | Desyrel, Oleptro |
| Trimipramine maleate | Surmontil |
| Venlafaxine hydrochloride | Effexor |

## Listing 8 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Mood Stabilizers (Listing 8 continued)** | |
| Carbamazepine | Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR |
| Lamotrigine | Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR |
| Valproic acid | Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate |
| **Antipsychotics** | |
| Acetophenazine | Tindal |
| Aripiprazole | Abilify |
| Asenapine | Saphris |
| Olanzapine | Zyprexa |
| Chlorpromazine | Thorazine |
| Haloperidol | Haloperidol, Haldol |
| Clozapine | Clozaril, Fazaclo |
| Fluphenazine | Prolixin |
| L-Methylfolate | Deplin, L-Methylfolate Calcium |
| Loxapine | Loxitane |
| Mesoridazine | Serentil |
| Perphenazine | Trilafon |
| Quetiapine | Seroquel |
| Risperidone | Risperdal |
| Thioridazine | Mellaril |
| Thiothixene | Navane |
| Trifluoperazine | Stelazine |
| **Benzodiazepines** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Estazolam | ProSom |

## Listing 8 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |
| Lorazepam | Ativan |
| Midazolam | Versed |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zopiclone | Imovane, Zimovane |
| Zopidem | Ambien, Ambien CR, Intermezzo, Stilnox, Stilnoct, Sublinox, Hypnogen, Zolsana |

Note: This list is not exhaustive.

PRN = Pro re nata

# Appendix 3 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

## Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

## Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In

this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

### Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

### Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed

scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

# Appendix 4 AEs Indicating Signals of Possible Drug Abuse Potential

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| 1 | **Euphoric mood** | Euphoric mood |
| | | Euphoria |
| | | Euphoric |
| | | Exaggerated well-being |
| | | Excitement excessive |
| | | Feeling high |
| | | Felt high |
| | | High |
| | | High feeling |
| | | Laughter |
| 2 | **Elevated mood** | Elevated mood |
| | | Mood elevated |
| | | Elation |
| 3 | **Feeling abnormal** | Feeling abnormal |
| | | Cotton wool in head |
| | | Feeling dazed |
| | | Feeling floating |
| | | Feeling strange |
| | | Feeling weightless |
| | | Felt like a zombie |
| | | Floating feeling |
| | | Foggy feeling in head |
| | | Funny episode |
| | | Fuzzy |
| | | Fuzzy head |
| | | Muzzy head |
| | | Spaced out |
| | | Unstable feeling |
| | | Weird feeling |
| | | Spacey |
| 4 | **Feeling drunk** | Feeling drunk |
| | | Drunkenness feeling of |
| | | Drunk-like effect |
| | | Intoxicated |
| | | Stoned |
| | | Drugged |
| 5 | **Feeling of relaxation** | Feeling of relaxation |
| | | Feeling relaxed |
| | | Relaxation |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Relaxed |
| | | Increased well-being |
| | | Excessive happiness |
| **6** | **Thinking abnormal** | Thinking abnormal |
| | | Abnormal thinking |
| | | Thinking irrational |
| | | Thinking disturbance |
| | | Thought blocking |
| | | Wandering thoughts |
| **7** | **Hallucination** | Hallucination |
| | | Illusions |
| | | Flashbacks |
| | | Floating |
| | | Rush |
| | | Feeling addicted |
| **8** | **Inappropriate affect** | Elation inappropriate |
| | | Exhilaration inappropriate |
| | | Feeling happy inappropriately |
| | | Inappropriate affect |
| | | Inappropriate elation |
| | | Inappropriate laughter |
| | | Inappropriate mood elevation |
| **9** | **Mood disorders and disturbances** | Mental disturbance |
| | | Depersonalisation |
| | | Psychomotor stimulation |
| | | Mood disorders |
| | | Emotional and mood disturbances |
| | | Delirium |
| | | Delirious |
| | | Mood altered |
| | | Mood alterations |
| | | Mood instability |
| | | Mood swings |
| | | Emotional lability |
| | | Emotional disorder |
| | | Emotional distress |
| | | Personality disorder |
| | | Impatience |
| | | Abnormal behavior |
| | | Delusional disorder |
| | | Irritability |
| **10** | **Drug tolerance** | Drug tolerance |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Habituation |
| | | Drug withdrawal syndrome |
| | | Substance-related disorders |
| **11** | **Psychosis** | Psychosis |
| | | Psychotic episode or disorder |
| **12** | **Dissociative State** | Dissociation |
| | | Disconnected |
| | | Derealisation |
| | | Depersonalisation |
| | | Detached |
| | | Sensation of distance from one's environment |
| | | Loss of a sense of personal identity |

# Appendix 5 Eisai Lymphocyte Subset Criteria for Study E2609-G000-202: Justification for a Population-Adjusted Approach

**Introduction:**

The Eisai clinical study, E2609-G000-202, requires the analysis of absolute numbers of various functional subsets of circulating lymphocytes. These are distinguished by identification of various complementary differentiation (CD) markers on the cell surface using fluorescent-labeled antibody reagents and flow cytometry. Current enumeration of certain lymphocyte subsets form part of the immunologically based eligibility criteria for study enrollment, as well as being monitored for safety for enrolled and treatment randomized subjects. The Trucount™ M (Becton, Dickinson and Company [BD], BD Biosciences, San Jose, CA) antibody reagents used for the lymphocyte subset eligibility criteria, provides readouts for both absolute (BD Trucount tubes) and percentage of lymphocyte subsets, and includes the following CD markers: CD3 (T cells), CD4 (T helper cells), CD8 (cytotoxic T cells), CD16/56 (natural killer cells), CD14 (macrophages), and CD19 (B cells).

Trucount lymphocyte subset reference ranges provided by the reagent manufacturer (BD) for both absolute and percentages were established for clinical use as an in vitro diagnostic using standardized reference interval methodology. These LLN for the various lymphocyte subsets are currently being used by the central laboratory for Eisai Study E2609-G000-202 to determine eligibility of screened subjects and as part of safety assessments during post-randomization visits. The eligibility criterion excludes subjects with absolute counts of T and B cell markers (CD4, CD8, and CD19 respectively) less than the reference range lower limit of normal (<LLN) at Screening or Baseline.

**Need to assign age appropriate reference ranges:**

Reference ranges established by the vendor according to working group guidance[3] may not be representative of different subgroup analyses (eg, ancestry, disease state, age, gender, etc.), and therefore interval adjustment may be required depending on the subpopulation of interest. The working group guidance for reference intervals (CLSI, 2010[4]) recommends examining data to determine if >10% of subjects are outliers (ie, more than 10% < LLN), and if so, to initiate development of subgroup-appropriate intervals by analyzing data from the literature or internal studies representing the reference population [a minimum of 120 observations recommended by the guidance.[3]]

Data from the ongoing Study E2609-G000-202 has been examined and greater than 10% of the study population screening samples fall below the manufacturer recommended LLN for the key lymphocyte subsets. The population for Study E2609-G000-202 are patients aged 50 to 85 years old inclusive with Mild Cognitive Impairment due to AD or with Mild to Moderate dementia due to AD. Lymphocyte subset data from a data cut of 93 screened

subjects was analyzed and showed that both CD8 and CD4 had greater than 10% of the subjects with results <LLN (26.9%, <220 cells/mm$^3$ and 13%, <404 cells/mm$^3$, respectively); CD19 had approximately 10% of the subjects with results <LLN (9.7%, <80 cells/mm$^3$).

To further determine if the outlier data observations from the ongoing Study E2609-G000-202 were associated with disease status or age, lymphocyte subset data from additional Eisai studies that included healthy elderly subjects or patients diagnosed with MCI or mild/moderate AD were examined. The individuals from all 3 studies included the same 50-to 85-year-old age range as the current E2609-G000-202 study. The studies evaluated include: (1) Study E2609-A001-002 treatment study (n=50 healthy elderly); (2) Lymphocyte subset pilot study in healthy elderly [n=30]; and (3) Lymphocyte subset pilot study in AD/MCI [n=31]. Screening or baseline sample from all 4 studies had >10% of the CD8 absolute counts below reference LLN, 2 out of 4 had >10% of the CD19 absolute counts below reference LLN and 1 out of 4 had >10% of the CD4 absolute counts out of reference LLN [Table 10, Table 11, and Table 12]. The data suggests that the reference values of LLN for CD4, CD8, and CD19 subsets are not a disease-associated observation but are related to the age of the study population being evaluated.

In addition to the Eisai study data, age related decline in lymphocyte subsets has been described in the literature Yan et.al.[1][2] Analysis was performed using flow cytometry on peripheral blood leukocytes using healthy subjects across the 3rd and 10th decades of life. The results from the Yan study (n=80; 37 males, 43 females) demonstrated that with advancing age there was a significant decline in the percentage of lymphocytes, specifically naive T cells [CD3 *P*=0.03], cytotoxic T cells [CD8 *P*=0.08] and activated B cells [CD20/CD69 *P*=0.03] with certain subsets demonstrating even greater decline in males.[1] The age associated changes in immune capabilities, termed “immunosenescence”, which include degenerative changes in the lymph nodes, effects on lymphocyte subsets and changes in adaptive immunity may underlie the increased risk of infection and cancer and decreased immune function in the elderly. This, along with the data from the four Eisai studies described earlier, support the readjustment of the LLNs for the CD reference ranges used for eligibility in Study E2609-G000-202 such that they are better suited to the older patient population enrolling in this study which is thought to be representative of the wider patient population.

**Determining the new LLN criteria:**

The recommended method for establishing reference intervals is the nonparametric approach where the underlying distribution of the data does not matter. The values received from the data (a minimum of 120 observations representing the subgroup population of interest is recommended) are rank ordered and can be used to evaluate the comparative reference interval.[3]

When data from the 4 Eisai studies are put in rank order (see Table 10, Table 11, and Table 12), and a 10% cut value is applied to each of the 3 CD markers of interest the following age-adjusted LLN values are generated:

**Table 9 Summary of CD4, CD8, and CD19 LLNs and Age-Adjusted LLNs**

| Lymphocyte Subset | Current LLN | Age-adjusted LLN |
|---|---|---|
| CD4 absolute count | 404 cells/$mm^3$ | 396 cells/$mm^3$ |
| CD8 absolute count | 220 cells/$mm^3$ | 157 cells/$mm^3$ |
| CD19 absolute count | 80 cells/$mm^3$ | 74 cells/$mm^3$ |

**Table 10 Summary of CD Counts (Parameter: CD19)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 30 | 203 |
| Mean | 213.47 | 198.49 | 159.20 | 172.77 | 192.57 |
| Median | 189.66 | 163.00 | 118.50 | 159.50 | 164.86 |
| 5th percentile | 84.81 | 59.00 | 38.00 | 69.00 | 59.00 |
| 10th percentile | 102.26 | 81.00 | 42.00 | 70.50 | 74.00 |
| 25th percentile | 139.66 | 104.00 | 75.00 | 100.00 | 104.58 |
| 75th percentile | 261.51 | 225.00 | 225.00 | 246.00 | 246.00 |
| 95th percentile | 376.67 | 443.00 | 424.00 | 384.00 | 402.00 |
| Range | 66.19, 593.48 | 17.00, 1066.00 | 37.00, 455.00 | 39.00, 415.00 | 17.00, 1066.00 |

**Table 11 Summary of CD Counts (Parameter: CD8)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 31 | 204 |
| Mean | 362.72 | 352.18 | 324.63 | 427.74 | 362.20 |
| Median | 364.74 | 330.00 | 344.00 | 315.00 | 336.39 |
| 5th percentile | 115.02 | 138.00 | 86.00 | 100.00 | 115.02 |
| 10th percentile | 170.24 | 151.00 | 159.50 | 153.00 | 157.00 |
| 25th percentile | 253.37 | 213.00 | 204.00 | 217.00 | 230.00 |
| 75th percentile | 465.52 | 425.00 | 405.00 | 494.00 | 438.00 |
| 95th percentile | 614.57 | 716.00 | 557.00 | 988.00 | 702.00 |

**Table 11 Summary of CD Counts (Parameter: CD8)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| Range | 98.45, 702.50 | 37.00, 803.00 | 61.00, 702.00 | 54.00, 2255.00 | 37.00, 2255.00 |

**Table 12 Summary of CD Counts (Parameter: CD4)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 31 | 204 |
| Mean | 846.15 | 839.58 | 789.27 | 804.52 | 828.46 |
| Median | 836.94 | 805.00 | 777.50 | 771.00 | 791.50 |
| 5th percentile | 388.44 | 337.00 | 395.00 | 351.00 | 344.00 |
| 10th percentile | 479.55 | 361.00 | 490.00 | 427.00 | 396.00 |
| 25th percentile | 639.54 | 620.00 | 661.00 | 669.00 | 633.77 |
| 75th percentile | 1031.49 | 1078.00 | 924.00 | 1014.00 | 1039.50 |
| 95th percentile | 1315.55 | 1404.00 | 1124.00 | 1327.00 | 1347.00 |
| Range | 274.90, 1643.55 | 197.00, 1481.00 | 248.00, 1720.00 | 143.00, 1336.00 | 143.00, 1720.00 |

References:

1. Yan et al., Immunity and Ageing 2010 v. 7:4; The effect of ageing on human lymphocyte subsets: comparison of males and females.
2. Wikby et al., Biogerontology 2008 vol 9: 299; The immune risk profile is associated with age and gender: findings from three Swedish population studies of individuals 20-100 years of age.
3. Horowitz eJIFCC 2008 vol. 19 (2) Reference intervals: practical aspects).
4. Horowitz et al., CLSI Vol 28 no. 30 Clinical and Laboratory Standards Institute's (CLSI) newly revised document Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition (C28-A3), published in November 2010 EP28-AC3

# PROTOCOL SIGNATURE PAGE

**Study Protocol Number:** E2609-G000-202
**Study Protocol Title:** A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability and Efficacy of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01)
**Investigational Product Name:** E2609
**IND Number:** 109308
**EudraCT Number:** 2014-002723-94

**SIGNATURES**
Authors:

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Date

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PPD Neuroscience and General Medicine Product Creation Unit
Eisai Ltd.

Date

PPD

Neuroscience and General Medicine Product Creation Unit
Eisai Inc.

Date

# INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability and Efficacy of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01) |
| **Investigational Product Name:** | E2609 |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

| Investigator | Signature | Date |
|---|---|---|

# REVISION HISTORY

**Revisions to Version 4.0**

**New version/date: Version 5.0, 06 Feb 2016**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Add interim analyses of safety, and PK/PD data throughout Stage A | Decision making regarding the remainder of the study and the full E2609 clinical development program | • Synopsis –<br>  ○ Study Design<br>  ○ Interim Analysis<br>• Section 9.1<br>• Section 9.4.6<br>• Section 9.7.3 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Grammatical, typographical, and formatting changes | | Throughout |
| Mandatory nature of CSF collection in study changed to voluntary. This change impacts the timing and details of the PK/PD interim analyses. It also impacts the nature of the CSF-related objectives, which will now be identified as exploratory. | To increase rate of subject consent into the study | • Synopsis –<br>o Secondary Objectives<br>o Exploratory Objectives<br>o Study Design<br>o Exclusion Criterion No. 12<br>o Pharmacokinetic Assessments<br>o Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments<br>o Safety Assessments<br>o Secondary Endpoints<br>o Exploratory Endpoints<br>o Analysis for the Secondary Endpoints<br>o Analysis for the Exploratory Endpoints<br>• Section 5.3<br>• Section 8.2<br>• Section 8.3<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.2.6<br>• Section 9.3.2<br>• Section 9.4.6<br>• Section 9.5.1.3.3<br>• Section 9.5.1.4<br>• Section 9.5.1.5.12<br>• Section 9.7.1.1.2<br>• Section 9.7.1.1.3<br>• Section 9.7.1.6.2<br>• Section 9.7.1.6.3<br>• Section 12, Listing 2 |
| Extended the range of cognitive impairment in delayed recall that would be considered inclusionary for the study and removed the eligibility nature of the cognitive tests repeated at the Baseline Visit. | Original delayed recall aspect of inclusion criterion #1 was considered to be too restrictive and was unnecessarily screening out subjects with | • Synopsis –<br>o Inclusion/ Exclusion Criteria<br>• Section 9.3.1<br>• Section 9.3.2 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | MCI/prodromal AD. The eligibility nature of the cognitive tests repeated at the Baseline Visit has been removed in order to simplify the requirements of the pretreatment period for the study. | |
| Addition of historical amyloid PET scans for determination of eligibility for the study. Subjects with historical PET scans will not be part of the longitudinal PET analyses and therefore will not require a second PET scan at either Visit 18 or ED. | To provide the sites with greater operational flexibility and reduce subject burden. | • Synopsis –<br>  ○ Inclusion/ Exclusion Criteria<br>  ○ Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments<br>• Section 9.1.1<br>• Section 9.2.5.3<br>• Section 9.3.1<br>• Section 9.5.2, Table 6 and Table 7 |
| Added the need for safety laboratory tests to be repeated for subjects whose pre-treatment period is extended due to active infection. | To ensure that all baseline safety laboratory tests are repeated for subjects whose pretreatment period is extended. | • Synopsis –<br>  ○ Inclusion/ Exclusion Criteria<br>• Section 9.3.2<br>• Section 9.5.2, Table 6 |
| Clarified that exclusion criterion No. 22 (exclusion of subjects with CD4, CD8, or CD19 absolute counts below the LLN) applies to flow cytometry tests conducted at both the Screening and the Baseline Visits. Furthermore, LLNs that are adjusted for the subject population under study will be used. | It was not clear that Exclusion Criterion No. 22 applied to both the Screening and the Baseline Visits. The LLNs for CD4, CD8 and CD19 absolute counts require adjustment for the age of the patient population in this study. | • Synopsis –<br>  ○ Inclusion/ Exclusion Criteria<br>• Section 9.3.2 |
| Provided additional detail regarding scope of Exclusion Criterion No. 34 which excludes subjects with hypopigmentation conditions. | Added to provide clarity for the sites. | • Synopsis –<br>  ○ Exclusion Criteria<br>• Section 9.3.2 |
| Revised number of clinical sites from 30 to 40 | For feasibility purposes | • Synopsis – Sites<br>• Section 6<br>• Section 9.1 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | | • Section 9.3 |
| Relaxed the requirement for the cognitive assessments at Screening Visit 1 to be conducted in a certain order and revised the recommended order in which the assessments could be conducted. | To provide the sites with greater operational flexibility. | • Section 9.1.1, Figure 2<br>• Section 9.5.1.3.1<br>• Section 9.5.2, Table 6 |
| Clarify the duration for which the Safety magnetic resonance imaging (MRI) scan, the amyloid PET scan and the lumbar puncture (LP) collected CSF conducted at Screening are considered valid. | To provide sites with greater operational flexibility, particularly for re-screening of screen fail subjects. | • Section 9.1.1 |
| Clarify that for subjects meeting criteria for weekly monitoring of lymphocyte subsets, these can be accommodated within the scheduled clinic visits during the early stages of the treatment period of the study. | To provide operational clarity to the sites. | • Synopsis –<br>o Exclusion Criteria<br>• Section 9.3.2<br>• Section 9.3.3<br>• Section 9.5.1.5.3 |
| Added the requirement for complete blood counts (CBC) with differentials to be performed whenever repeat or unscheduled flow cytometry tests are performed. | Such that CBC data are available at all times when flow cytometry data is available. | • Section 9.3.3, Table 1<br>• Section 9.5.2,<br>o Table 6<br>o Table 7 |
| Added 30 day window to the duration of the pre-treatment period if required for medical or operational reasons. | To provide the sites with greater operational flexibility. | • Synopsis –<br>o Study Design<br>o Duration of Treatment<br>• Section 9.1, Figure 1<br>• Section 9.1.1<br>• Section 9.1.1.2<br>• Section 9.5.2, Table 6 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Clarified the timing of the start of the Randomization Phase | Clarification | • Section 9.1.1<br>• Section 9.1.2<br>• Section 9.5.2,<br>o Table 6<br>o Table 7 |
| Increased number of MCI/Prodromal or mild to moderate AD subjects screened for entry into the study | To reflect the higher screen failure rate than originally anticipated | • Synopsis –<br>o Number of Subjects |
| Removal of CD127 cell surface markers | FoxP3 is the most accepted marker to measure T regulatory cells and additional assessment of CD127 is not required. | • Section 9.5.1.5.3, Table 4<br>• Section 9.5.2.1 |
| Made the clinical biochemistry, urinalysis, CBC, lymphocyte subsets, and immunoglobulin tests mandatory at Visit 20, regardless of clinical significance at Visit 19. | For more comprehensive safety data at the second follow-up visit. | • Section 9.5.2, Table 7 |
| Corrected reference to Exclusion Criterion No. 20 (and not to Exclusion #19) in footnote to Table 6 and Table 7 regarding timing of Visit 3 in relation to Visit 2. | Correction | • Section 9.5.2,<br>o Table 6<br>o Table 7 |
| Revised details regarding prohibited antiplatelet drugs | To distinguish between those subjects who consent to CSF sample collection and those who do not | • Appendix 2, Listing 2 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised inclusion to allow for enrollment of mild to moderate AD subjects in Stage A and expand the Stage B mild AD cohort to also include moderate AD subjects | To collect safety data in a wider range of AD patients. | • Title Page<br>• Synopsis –<br>  ○ Objectives<br>  ○ Study Design<br>  ○ Number of Subjects<br>  ○ Inclusion/Exclusion Criteria<br>  ○ Study Treatments<br>  ○ Efficacy Assessments<br>  ○ Study Endpoints<br>  ○ Efficacy Analyses<br>  ○ Interim Analyses<br>  ○ Adaptive Randomization<br>  ○ Sample Size<br>• Section 5.3<br>• Section 7<br>• Section 8 (and all subsections)<br>• Section 9.1, Section 9.1.1<br>• Figure 1<br>• Section 9.2.1, Section 9.2.2, Section 9.2.3<br>• Section 9.2.5.3 and Section 9.2.5.4<br>• Section 9.3, Section 9.3.1, Section 9.3.2<br>• Section 9.4.1, Section 9.4.3, Section 9.4.4<br>• Section 9.5.1.3.1<br>• Section 9.7.1.1.2, Section 9.7.1.1.3<br>• Section9.7.1.4<br>• Section 9.7.1.6, Section 9.7.1.6.2, Section 9.7.1.6.3<br>• Section 9.7.1.8.2<br>• Section 9.7.2.2<br>• Section 9.7.3<br>• Section 9.7.4 |
| Revised inclusion criteria for MMSE to ≥16 from ≥20 | The MMSE score is used as a cut-off for the most impaired subject that would be eligible for the study. Lowering the MMSE inclusion from ≥20 to ≥16 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD cohort. | • Synopsis – Inclusion/Exclusion Criteria<br>• Section 9.3.1 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised inclusion criteria for FAQ to ≤24 from ≤20 | As for the MMSE, the FAQ score is used as a cut-off for the most impaired subject that would be eligible for the study. Revising the FAQ inclusion from ≤20 to ≤24 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD cohort, and is consistent with an MMSE inclusion of ≥16. | • Synopsis – Inclusion/Exclusion Criteria<br>• Section 9.3.1 |
| Revised exclusion criteria such that small arachnoid cysts are not necessarily exclusionary | Arachnoid cysts are a common finding in otherwise healthy subjects. Small lesions (<1 cm in diameter) are generally not considered clinically significant and if discovered incidentally no long term follow up is routinely required. | • Synopsis – Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised exclusion criteria for Ig (IgG, IgA, or IgM) to specify that levels below the LLN at Screening or Baseline need not be exclusionary | For subjects with a Screening or Baseline IG level <LLN to be considered for continuation in the study, assessment of clinical significance of the finding will be required. A finding of "not clinically significant" must be agreed between the Investigator and Medical Monitor in order for the subject to continue in the study. | • Synopsis – Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised text to provide instructions for subject assent and associated consent by a legal representative for subjects who the Investigator considers not to have the capacity to consent themselves | With the expansion of the patient population to include moderately demented subjects it was necessary to provide directions regarding the consenting process for subjects considered to be lacking the capacity to consent themselves. | • Section 5.3 |
| Revised number of clinical sites to 30 from 25 | For feasibility purposes. | • Synopsis – Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Added allowance for Tier 1 and Tier 2 screening assessments to be performed on the same day | Added to provide operational clarity for the sites. | • Section 9.1.1.1<br>• Table 6 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Removed requirements for MRIs to include sequences for resting state functional MRI | This was an error and should not have been included in the original protocol. | • Table 6<br>• Table 7 |
| Revised text to clarify that on visits where CSF collection takes place, the CSF collection need not take place on the same day as the cognitive testing for that visit | Added to provide operational clarity for the sites. | • Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised text to clarify that the most important efficacy assessment to keep blinded from safety data is the CDR. | Added to provide operational clarity for the sites. | • Synopsis – Safety Assessments<br>• Section 9.4.6<br>• Section 9.5.1.5 |
| Revised text to allow PK blood sample and PD blood samples to be taken either shortly before or shortly after the LP on CSF days | Added to provide operational flexibility for the sites. | • Section 9.5.1.4.1<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised Sponsors Grading for Laboratory Values for the following analytes: lymphocytes, neutrophils, albumin, creatinine, phosphate, and potassium serum-high (hyperkalemia) | Corrections made to align with the values for grading used by the central clinical laboratory for this study. | • Appendix 1 |
| Revised details regarding prohibited antiplatelet drugs | Previous version incorrectly referenced a biomarker subgroup. All subjects in this study will need to provide CSF samples. | • Appendix 2; Listing 2 |
| Revised grammar, spelling, etc. | Compliance with current company style guide and for general consistency. | Throughout protocol |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revisions to grammar, spelling, etc. | Compliance with current company style guide and for general consistency | • Throughout protocol |
| Revisions made per new company protocol template | Alignment with current Eisai template | • Synopsis - Inclusion/Exclusion Criteria<br>• Section 9.1.2.3<br>• Section 9.3.1<br>• Section 9.3.2<br>• Section 9.5.1 (related subsections)<br>• Section 9.5.4<br>• Section 9.5.4.1<br>• Section 9.5.4.2<br>• Section 9.5.4.3 |
| Clarified classification of MCI due to AD | Clarification that MCI due to AD population will also be consistent with the research criteria for Prodromal AD in that impaired episodic memory is required and will be tested using a list learning task (the International Shopping List Task) | • Synopsis – Study Design<br>• Section 9.1 |
| Replaced “enroll” with “randomize,” pertaining to subject entry into study | Correction to terminology | • Synopsis – Study Design<br>• Section 9.1<br>• Section 9.3 |
| Added criterion excluding subjects with hepatic impairment and total bilirubin greater than 1.5×ULN or INR greater than 1.7 at Screening or Baseline. Subjects with Gilbert’s syndrome need not be excluded. | At request of FDA, exclude subjects who have hepatic impairment | • Synopsis – Inclusion/Exclusion Criteria<br>• Abbreviation List<br>• Section 9.3.2 |
| Added coagulation parameters for prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR) to screening and baseline procedures | Screen for hepatic impairment | • Synopsis – Inclusion/Exclusion Criteria<br>• Abbreviation list<br>• Section 9.3.2<br>• Table 4<br>• Table 6<br>• Table 8 |
| For subjects who discontinue study drug prematurely, conduct efficacy | To facilitate efficacy analyses, which are based on longitudinal | • Synopsis –Study Design<br>• Section 9.1.2.2<br>• Section 9.3.3 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| assessments postdose at same time points as subjects who continue in the study. Added FAQ to this set of efficacy assessments. | modeling for all subjects | • Section 9.5.4.1<br>• Section 9.5.5<br>• Table 7 |
| Delete diagram of E2609 structure | This display is not needed for the protocol. The Investigator's Brochure has this information. | • Section 9.4.2.1 |
| Additional blood samples to be taken at Visits 19 and 20 | Samples are to be put in storage to allow for assessment of immune status at end of study, as needed. | • Synopsis - Assessments<br>• Table 8 |
| Add subheadings to Section 9.7 describing the primary endpoint analysis, and text clarifying that no multiplicity adjustments will be done to account for the interim analyses | To distinguish clearly the primary analysis and the sensitivity analyses of the primary endpoint | • Synopsis - Efficacy Analyses<br>• Section 9.7.1.6.1 |
| Clarification of PK sampling upon Early Discontinuation | Additional operational details of the timing of the PK sampling at the ED visit provided | • Section 9.5.1.4.1<br>• Table 7 |
| Clarification of ApoE testing | Clarification that the ApoE genetic testing will be for homozygous or heterozygous E4, versus non-E4 | • Section 9.5.1.4.2 |
| Revision to PK/PD interim analysis text | Confirm that interim PK/PD analysis will be conducted by an independent group | • Section 9.4.6 |
| Addition of text regarding safety signals with E2609 | To provide information on safety-driven dose adjustments | • Synopsis – Study Design<br>• Section 9.1 |
| Addition of PBMC collection/assessment at Baseline, during treatment, and posttreatment | Recent animal studies have shown an effect of E2609 on this model so they will be added to the 202 clinical study as an additional exploratory assessment. | • Synopsis – Safety Assessments<br>• Section 9.2.6<br>• Section 9.5.1.5<br>• Table 4<br>• Table 6<br>• Table 7<br>• Table 8 |
| Stipulate that exploratory biomarker analyses may be conducted using blood or CSF samples that may have been drawn for other purposes | To allow more flexibility for possible exploratory biomarker studies associated with study drug or disease, including miRNA and DNA | • Synopsis - Assessments,<br>• Abbreviation list<br>• Section 9.5.1.4.2<br>• Section 9.5.1.5.12<br>• Table 6<br>• Table 7 |
| Prohibit concomitant medications that are strong CYP3A4, inhibitors, but clarify that no restrictions are | At request of FDA, in light of finding that inhibition of CYP3A4 by a reference agent increases | • Synopsis - Concomitant Drug/Therapy<br>• Section 7.1 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| needed for other CYP3A4 inhibitors, CYP3A4 inducers, or CES2 inhibitors | plasma levels of E2609 | • Section 9.4.7<br>• Appendix 2(Listing 6) |
| Addition of tests for viral characterization at Baseline | To confirm by serology information of subjects prior exposure to common viruses pre-dosing with study drug | • Section 9.5.1.2.2<br>• Table 4<br>• Table 6<br>• Table 8 |
| Use of a centralized dermatologist assessment via photography | A centralized approach, using standardized photography, to FDA-required serial dermatological assessments will be employed for consistency of assessments between sites and for consistency of longitudinal assessments of individual subjects. | • Synopsis – Safety Assessments<br>• Section 9.2.6<br>• Section 9.5.1.5<br>• Section 9.5.1.5.8<br>• Table 6<br>• Table 7 |
| Removal of testing for benzodiazepines or opioids as part exclusion criteria #35 | To differentiate appropriate medicinal use from recreational drug use or abuse | • Synopsis – Exclusion Criteria<br>• Section 9.3.2 |
| Addition of analysis of other covariates such as adjusted hippocampal volume will be studied | Hippocampal volume has been shown to correlate with rate of cognitive decline and as such is a key covariate to be used in the analyses. | • Synopsis – Analysis of Primary Endpoint<br>• Section 9.7.1.6.1 |
| Addition of clarifications to ophthalmic examination | To provide more detail around the requirements for the ophthalmic exam | • Synopsis – Safety Assessments<br>• Section 9.5.1.5.13<br>• Table 6<br>• Table 7 |
| Addition of details regarding specific method of CSF collection (ie, gravity drip) | Use of materials required for suction method when collecting CSF can affect the PD data and so it is important to make it clear that only the gravity drip method can be used for collecting CSF in this study for protecting the quality and the consistency of the CSF PD data. | • Section 9.5.1.3.3<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Addition of specific testing for B12 levels at Screening | Abnormally low serum vitamin B12 levels are exclusionary for the study (exclusion criterion 8) but a blood draw for Vitamin B12 was inadvertently missed out of Table 6 in protocol version 1. | • Synopsis – Exclusion Criteria<br>• Section 9.3.2<br>• Section 9.5.1.2.3<br>• Figure 2<br>• Table 6 |
| Addition of details regard AEs that might be signals of possible drug abuse potential | Changed terminology re: collection of additional information for AEs that might be signals of possible | • Synopsis – Safety Assessments<br>• Section 9.2.6<br>• Section 9.5.1.5.1 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | abuse potential. No longer use the word "narrative" in order to avoid potential confusion with standard clinical trial narratives eg, for serious adverse events, adverse events leading to withdrawal, etc. | • Appendix 4 |
| Addition of clarification regarding position for taking vital signs (ie, supine) | The American Heart Association guidelines only mention supine, standing, and sitting as positions for taking HR and BP measurements. Therefore, have changed required position from semi-supine to sitting. | • Section 9.5.1.5.4<br>• Table 6<br>• Table 7 |
| Stipulated that study drugs are to be taken with food | For consistency of treatment conditions | • Section 9.5.1.4.1 |
| Change to list of Study Specific AEs which should be considered SAEs | Eisai's standard procedures have changed such that non-serious study specific adverse events of interest are no longer reported to Eisai Product Safety; instead, any additional information required for such non-serious adverse events will be obtained through other methods. In addition, certain events (new onset seizures, ocular herpes) are now to be classified as serious as important medical events, regardless of whether they meet standard ICH serious criteria. | • Section 9.5.1.5.1<br>• Section 9.5.1.5.2 |
| Increased blood volume for PK | To match collection tubes and ensure sufficient sample for planned assays | • Table 8 |
| Corrected error in definition of PK analysis set | For accuracy | • Synopsis – Study Endpoints<br>• Section 9.7.1.2 |
| Addition of details regarding discontinuation of study drug | To clearly and consistently differentiate "discontinuation from study drug" from "withdrawal from study" | • Synopsis<br>• Section 7<br>• Section 9.1.2.1<br>• Section 9.2.6<br>• Section 9.3.3<br>• Table 1<br>• Table 2<br>• Section 9.4.1<br>• Section 9.4.4<br>• Section 9.5.1.5.1<br>• Section 9.5.1.5.3<br>• Section 9.5.5 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Re-ordered prohibited medication lists | For consistency, all lists re-ordered in alphabetical order of generic drug name, and footnotes revised for overall consistency | • Appendix 2 |
| Moved nefazodone from Listing 9 to Listing 6 | Nefazodone is a strong CYP3A4 inhibitor and is therefore prohibited. | • Appendix 2 |

# 1 TITLE PAGE


## Clinical Study Protocol

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability, and Efficacy of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01) |
| **Sponsor:** | Eisai Inc.<br>155 Tice Boulevard<br>Woodcliff Lake,<br>New Jersey 07677<br>United States<br><br>Eisai Ltd.<br>European Knowledge Centre<br>Mosquito Way<br>Hatfield, Hertfordshire<br>AL10 9SN<br>United Kingdom<br><br>Eisai Co., Ltd.<br>4-6-10 Koishikawa<br>Bunkyo-Ku,<br>Tokyo 112 8088<br>Japan |
| **Investigational Product Name:** | E2609 |
| **Indication:** | Alzheimer's disease |
| **Phase:** | 2 |
| **Approval Date:** | V1.0 15 Jul 2014 (original protocol)<br>V2.0 21 Oct 2014 (revised original protocol)<br>V3.0 28 May 2015 (Amendment 01)<br>V4.0 05 Nov 2015 (Amendment 02)<br>V5.0 06 Feb 2016 (Amendment 03) |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |
| **GCP Statement:** | This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities. |
| **Confidentiality Statement:** | This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study. |

# 2 CLINICAL PROTOCOL SYNOPSIS

**Compound No.:**

E2609

**Name of Active Ingredient:**

*N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

**Study Protocol Title**

A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability, and Efficacy of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01)

**Investigators**

Stage A: Investigators in United States only

Stage B: Multinational investigators

**Sites**

Stage A: Approximately 40 sites, United States only (revised per Amendments 01 and 02)

Stage B: Approximately 125 sites, globally

**Study Period and Phase of Development**

Stage A: Approximately 32 months and will continue and overlap with Stage B

Stage B: Approximately 42 months from initiation of Stage B (revised per Amendment 01)

Phase 2

**Objectives**

**Primary Objectives**

1. To evaluate the efficacy of daily dosing with 3 doses of E2609 compared with placebo by establishing the lowest effective dose that achieves 90% of the greatest treatment effect ($ED_{90}$) for E2609 on the derived Alzheimer's Disease Composite Score (ADCOMS) at 18 months of treatment in subjects with Mild Cognitive Impairment due to Alzheimer's Disease/ Prodromal Alzheimer's Disease (referred to as MCI/Prodromal throughout the protocol)
2. To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with Mild to Moderate Dementia due to Alzheimer's Disease (referred to as mild to moderate AD throughout the protocol) (revised per Amendment 01)

**Secondary Objectives** (revised per Amendment 02)

1. To evaluate the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects, as measured by volumetric magnetic resonance imaging (vMRI)
2. To evaluate the efficacy of E2609 compared with placebo on the derived ADCOMS at 18 months in mild to moderate AD subjects (revised per Amendment 01)

**Exploratory Objectives**

(revised per Amendments 01 and 02)

1. To explore the effect of E2609 compared with placebo on the derived ADCOMS following 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
2. To explore the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in mild to moderate AD subjects, as measured by vMRI
3. To explore the effects of E2609 compared with placebo on Aβ(1-x) and Aβ (1-42) in CSF after 4 weeks and 18 months of treatment in MCI/Prodromal subjects and in mild to moderate AD subjects (revised per Amendment 02)
4. To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during post-treatment follow-up, in MCI/Prodromal and mild to moderate AD subjects, by assessment of:
   a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
   b. The Clinical Dementia Rating (CDR) scale
   c. The Mini-Mental State Examination (MMSE)
   d. The CogState Brief Battery (CBB)
   e. The Functional Assessment Questionnaire (FAQ; also known as the Functional Activities Questionnaire)
   f. The International Shopping List Task (ISLT)
5. To explore the effects of E2609 compared with placebo on various biomarkers in MCI/Prodromal and mild to moderate AD subjects. Biomarkers to be explored include:
   a. CSF biomarkers of neurodegeneration (eg, tau, phosphorylated-tau [p-tau]) after 18 months of treatment
   b. Plasma and CSF amyloid, and CSF β-amyloid converting enzyme 1 (BACE1) measurements during 18 months of treatment and during posttreatment follow-up
   c. vMRI measurements including left and right hippocampal volume, whole brain volume and total ventricular volume at 6, 12, and 18 months of treatment and during posttreatment follow-up
   d. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)
6. To characterize the population pharmacokinetics (PK) of E2609 in MCI/Prodromal and mild to moderate AD subjects, and to examine the effect of intrinsic and extrinsic factors (including N-acetyltransferase 2 [*NAT2*] phenotype) on the PK
7. To explore the relationship between the treatment effects of E2609 on the ADCOMS and its effects on CSF amyloid, CSF BACE1, CSF tau, and vMRI in MCI/Prodromal and mild to moderate AD subjects

**Study Design**

This will be a multicenter placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild to moderate AD. A common set of inclusion criteria, consistent with the National Institute on Aging – Alzheimer's Association (NIA-AA) clinical research criteria for Mild Cognitive Impairment (MCI) due to Alzheimer's Disease (AD) or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with the criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal

subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study will be conducted in 2 stages, Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 (after the first 60 randomized subjects have completed 12 weeks of treatment or have discontinued study drug early) before expanding enrollment to include a larger number of subjects in Stage B. (revised per Amendment 01) All MCI/Prodromal subjects will be included in the primary efficacy evaluation irrespective of whether they were recruited during Stage A or Stage B. Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B. All mild to moderate AD subjects will be included in the efficacy evaluations for that cohort. (revised per Amendment 01)

Both Stage A and Stage B will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days, plus an additional window of up to 30 days if required [revised per Amendment 02]) includes a Screening Visit (Visit 1) and a Baseline Visit (Visit 2). All screening assessments (within 4 distinct tiers) must be completed, and eligibility to continue in the study confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

**Stage A**

Stage A will be limited to approximately 40 sites in the United States. (revised per Amendments 01 and 02) Stage A will randomize 60 eligible subjects at Visit 3, 1:1:1:1 to 4 treatment groups within each of the 2 clinical populations. (revised per Amendment 01) In addition to the placebo group, 3 E2609 doses will be used to reduce CSF amyloid β levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/pharmacodynamic (PD) modeling has shown that these doses should achieve these targets when administered once daily (QD) with food, and these doses will be evaluated based on the 4-week assessment of CSF Aβ(1-x) from subjects who provide voluntary consent for CSF measurement. (revised per Amendment 02)

During Stage A, safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the first subject is randomized during Stage A, an independent data safety monitoring board (DSMB; including at least 1 immunologist) will review all safety data in an unblinded manner. The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. Unless the DSMB recommends otherwise, randomization of subjects into Stage A will continue until 60 subjects have been randomized and dosed. (revised per Amendment 01)

Interim analyses of the E2609 PK and PD profiles will be performed on subjects who consent to provide CSF samples at Baseline and after 4 weeks of study drug. These interim analyses, as well as analyses of safety data, will be performed on an ongoing basis throughout Stage A. Refer to the Interim Analysis section for more detail. (revised per Amendment 03) These data will be used to evaluate the CSF PD effects of E2609 doses, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels. (revised per Amendments 01 and 02) The mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment for each dose of E2609 and its 90% confidence interval will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data from Stage A and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline after 4 weeks of dosing. (revised per Amendment 02)Once 60 subjects in Stage A have completed at least 12 weeks of treatment (or discontinued study drug early) an interim

safety analysis will be conducted by Eisai and the DSMB. (revised per Amendment 01) Subjects in Stage A will continue study drug while the DSMB reviews all the available safety data, but randomization of additional subjects will not take place (ie, recruitment into Stage B will not commence) until the safety analysis is completed by the DSMB.

If there are safety signals with one of the E2609 dose groups that would require dose adjustment, changes to dose will be reflected in an amendment to the protocol. Information on how these subjects will be handled in the primary analysis will be described in the Statistical Analysis Plan.

**Stage B**

Stage B will start after the DSMB safety review of Stage A has shown acceptable safety and tolerability of E2609 and after the doses of E2609 to be used in Stage B are evaluated. (revised per Amendment 02) Stage B will enroll, randomize, and dose additional eligible subjects up to a maximum of 500 MCI/Prodromal and up to a maximum of 200 mild to moderate AD. The final total number of MCI/Prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. (revised per Amendment 01) Safety data from Stage B will continue to be reviewed by the DSMB (approximately every 3 months) until recruitment to the study is completed; following this the DSMB will meet approximately every 6 months.

In Stage B, both cohorts will include separate placebo groups. The MCI/Prodromal cohort will include 3 doses of E2609 (5, 15, and 50 mg QD) whereas the Mild to Moderate AD cohort will only include 2 doses of E2609 (15 and 50 mg QD). (revised per Amendment 01)

Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B. Randomization of MCI/Prodromal subjects into Stage B will commence according to a fixed schedule (1:1:1:1; placebo:5 mg E2609:15 mg E2609:50 mg E2609) until a total of 100 MCI/Prodromal subjects (including those from Stage A) have been randomized. (revised per Amendment 01) The remaining subjects in the MCI/Prodromal cohort in Stage B will then be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. The mild to moderate AD subjects will be randomized according to a fixed schedule (1:1:1 placebo; 15 mg E2609; 50 mg E2609) throughout Stage B. (revised per Amendment 01)

**Early Discontinuation**

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug. Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie, at Visits 11, 14, 15, 16, 17, and 18) if these visits have not already been performed. At these visits, only the clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB and ISLT) will be conducted. Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

**Follow-Up**

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug (Visit 19) and a second 12 weeks after the last dose of study drug (Visit 20). If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the posttreatment Follow-Up period.

**Number of Subjects**

- Stage A: Approximately 400 MCI/Prodromal or mild to moderate AD subjects will be screened to provide 60 randomized subjects (target of 15 subjects per treatment arm). There will be no limit to the number of subjects randomized from either clinical cohort. (revised per Amendments 01 and 02)
- Stage B: Up to approximately 2100 MCI/Prodromal subjects will be screened to provide up to 500 randomized subjects. The final number of MCI/Prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. In addition, up to approximately 835 subjects with mild to moderate AD will be screened to provide up to 200 randomized mild to moderate AD subjects. The final number of mild to moderate AD subjects randomized in Stage B will depend upon the number of mild to moderate AD subjects previously randomized during Stage A. (revised per Amendment 01)

**Inclusion Criteria**

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD or AD dementia and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at Screening Visit 1:**
(revised per Amendment 02)

   a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation
   b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT. Alternatively, cognitive impairment of at least 0.5 SD from age-adjusted norms in delayed recall on the ISLT plus impairment of at least 1 SD from age-adjusted norms in at least 1 other computerized learning and memory test (ISLT immediate recall, or 1 of the learning and memory components of the CBB). (revised per Amendment 02)
   c. FAQ $\leq$24 (revised per Amendment 01)
   d. MMSE $\geq$16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading; an historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group (revised per Amendment 02)
3. Male or female, age 50 to 85 years, inclusive at time of consent
4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.
5. If receiving acetylcholinesterase inhibitors (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.
6. Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization.

**Exclusion Criteria**

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or magnetic resonance imaging (MRI)

2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and < 1cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could, in the opinion of the investigator, confound the MCI/Prodromal or mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendments 01 and 02)
7. A score of ≥8 on the 15-item Geriatric Depression Scale at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the lower limit of normal (LLN) for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
12. Any contraindications to lumbar puncture for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity). Only applicable to subjects consenting to CSF sample collection (revised per Amendment 02)
13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles

18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization
20. Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below population-adjusted LLN at Screening or Baseline and confirmed by a repeat test conducted 1 week after the initial test. The population-adjusted LLN for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are 396, 157, and 74 cells/μL respectively. (revised per Amendment 02)
23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the Investigator and the Medical Monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of clinical immunodeficiency. The discussion with the Medical Monitor should include a detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)
24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate electrocardiograms (ECGs). A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute at Screening or Baseline
29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy;

these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.

33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo). Diagnosis of an underlying disease causing hypopigmentation is not necessary for exclusion if the clinical presentation is consistent with such a condition. Hypopigmentation associated with scarring need not be exclusionary. (revised per Amendment 02)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period and for 28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.

- Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
  (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

44. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or not practicing highly effective contraception throughout the study period or for 28 days after study drug discontinuation). No sperm donation is allowed during the study period or for 28 days after study drug discontinuation.

**Study Treatments**

E2609 tablets of 5-mg, 10-mg and 25-mg dose strengths will be supplied. Placebo tablets to match E2609 will be of identical appearance. Each subject will receive 2 tablets, which when combined will make up the required doses of E2609 (see below) or placebo, to be administered orally QD with food.

- Stage A: 3 doses (5, 15, and 50 mg) of E2609 or placebo (revised per Amendment 01)
- Stage B, MCI/Prodromal Cohort: 3 doses (5, 15, and 50 mg) of E2609 or placebo (revised per Amendment 01)
- Stage B, Mild to Moderate AD Cohort: 2 doses (15 and 50 mg) of E2609 or placebo. (revised per Amendment 01)

**Duration of Treatment**

The maximum duration of a subject's participation in the study will be approximately 2 years, comprising:

- Screening and Baseline Periods (Prerandomization Phase): up to 60 days, plus an additional window of up to 30 days if required (revised per Amendment 02)

  (In subjects who have an active infection within 4 weeks of the planned randomization date, the duration of the pre-randomization phase can be extended by up to 4 weeks to allow additional time for resolution of the infection.)
- Treatment Period (Randomization Phase): up to 78 weeks
- Follow-Up Period (Randomization Phase): 12 weeks (post last dose)

**Concomitant Drug/Therapy**

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit (see Appendix 2 for a detailed listing of these agents):

- Anticoagulants (eg, warfarin, digabatrin) are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization
- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization

Subjects taking AChEIs or memantine must meet the following criteria in order to be included in the primary analyses:

- On a stable dose for 12 weeks before the baseline cognitive assessments at Visit 2
- Remain on a stable dose while on study

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for the primary analyses.

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if, in the opinion of the investigator, this will not interfere with study procedures or subject safety, and are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks.

**Assessments**

**Efficacy Assessments**

Derived ADCOMS: The derived ADCOMS represents a new approach to the analysis of selected items (12 total) from 3 fully validated and well established clinical tools, the ADAS-cog (4 items), the MMSE (2 items), and the CDR (all 6 items). The 3 scales should be administered in full in the

morning, or, if not possible, consistently at the same time of day.

Alzheimer's Disease Assessment Scale - cognitive subscale: The 14-item version will be used since it is considered more relevant for subjects with MCI/Prodromal AD or mild AD.

Mini Mental State Examination: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing.

Clinical Dementia Rating: Assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

CogState Brief Battery: A computer-based battery comprising 4 cognitive tests:

1. Detection – a simple reaction time test. Speed of response is the measure.
2. Identification – a simple choice reaction time test. Speed of response is the measure.
3. One Card Back – a simple working memory test. Accuracy of response is the measure.
4. One Card Learning – a visual learning and memory test. Accuracy of response is the measure.

International Shopping List Task: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall.

Functional Assessment Questionnaire: The FAQ has 10 items concerned with performing daily tasks necessary for independent living. Either a caregiver or informant or the subject provides performance ratings on 10 complex activities of daily living performed within the preceding 4 weeks.

Volumetric Magnetic Resonance Imaging: vMRI will be used to evaluate disease modification, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs.

**Pharmacokinetic Assessments**

Blood samples will be collected for the determination of the concentrations of E2609. For subjects who consent to CSF sample collection, CSF samples will be collected for the determination of E2609 concentrations. (revised per Amendment 02) Analyses of metabolite concentrations may be performed depending on emerging data from other studies with E2609.

**Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments**

Brain atrophy will be measured by vMRI: see Efficacy Assessments (above).

The soluble biomarkers Aβ(1-x), Aβ(1-42), total tau (t-tau), and p-tau will be measured in subjects who consent to CSF sample collection (revised per Amendment 02). BACE1 levels and activity in CSF will also be measured in subjects who consent to CSF sample collection (revised per Amendment 02). Other exploratory biomarkers (eg, miRNA) may also be evaluated in plasma and/or CSF.

Amyloid PET imaging will be used to confirm that all subjects eligible for progression to the Baseline Period have amyloid deposition in the brain. An historical amyloid positive PET scan may be used, if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02) Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses) and will only be conducted through to the time at which acceptable 18-month PET scans have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used. (revised per Amendment 02)

Apolipoprotein E (*ApoE*) and *NAT2* genotyping/phenotyping will be conducted. *ApoE4* homozygous or heterozygous status versus non-carriers and *NAT2* status will be used in the statistical analysis to determine the effects on treatment response and safety. Remaining genomic DNA may also be stored for up to 15 years to be used to examine the role of DNA sequence variability on the absorption, distribution, metabolism, and elimination of E2609, development of AEs, as well as the underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single-nucleotide polymorphisms with PK, safety, or PD data.

**Safety Assessments**

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR. (revised per Amendment 01) Routine safety assessments will include the monitoring and recording all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

Complete blood counts and lymphocyte subset absolute counts and percentages will be measured (by a centralized laboratory) every week for the first month, every 2 weeks for the next 2 months (Months 2 and 3) and monthly for the next 3 months (Months 4, 5, and 6). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits. Serum IgG, IgA, and IgM will be monitored monthly for the first 3 months, at 6, 12, and 18 months, and at both Follow-Up Visits.

Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and posttreatment for exploratory immunomodulatory and immune-based analyses.

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at baseline and at 3-month intervals during the Treatment Period. These assessments will specifically include evaluation of any areas of depigmentation or rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregivers/ informants will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so such AEs can be reviewed promptly.

Baseline and on-study blood and DNA samples will be taken and stored for all subjects, and CSF samples will be taken and stored for all subjects who consent to CSF sample collection (revised per Amendment 02). These samples may be tested for exploratory biomarkers associated with study drug or disease, or in the event that a subject develops AEs that warrant further investigation (eg, to test if a subject with a treatment-emergent infection was exposed to any suspected infective agents before treatment with study drug).

Safety brain MRI assessments will be performed at Screening, at 6, 12, and 18 months during the Treatment Period and at the final Follow-Up Visit. Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Full neurological examinations will be performed at Baseline, at 6, 12, and 18 months, and at both Follow-Up Visits, by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations. The neurological examinations will include muscle strength

testing and assessment of cranial nerves including olfaction as well as other parts of the CNS.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments will include the ADAS-$cog_{14}$, MMSE, and CBB.

An assessment of suicidality using the C-SSRS will be performed at Screening and Baseline and at regular intervals throughout the Treatment and Follow-Up Periods.

An ophthalmic examination (including retinal examination) will be conducted at Baseline. An additional examination will be conducted if the subject experiences visual disturbances during the course of the study.

A number of safety-related criteria for discontinuation of study drug are specified for the study.

**Bioanalytical Methods**

Plasma and CSF concentrations of E2609 will be measured by a validated liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) in both CSF and plasma will be measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and post-screening analysis of CSF Aβ(1-42), tau, and p-tau will be performed using ELISAs.

BACE1 levels and activity may be measured using a customized assay. Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

**Statistical Methods**

All statistical tests will be based on the 5% (2-sided) level of significance, except for the Bayesian methods on the primary endpoint.

**Study Endpoints**

**Primary Endpoint**

- Change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects

**Secondary Endpoints**

Change from baseline in: (revised per Amendment 02)

- Total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- The derived ADCOMS at 18 months of treatment in mild to moderate AD subjects (revised per Amendment 01)

**Exploratory Endpoints**

(revised per Amendments 01 and 02)

Change from baseline in:

- The derived ADCOMS at 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
- Total hippocampal volume at 12 and 18 months of treatment in mild to moderate AD subjects as measured by vMRI

- CSF Aβ(1-x) and Aβ(1-42) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects and in mild to moderate AD subjects (revised per Amendment 02)
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ in MCI/Prodromal and mild to moderate AD subjects
- CSF biomarkers of neurodegeneration (eg, tau and p-tau) at 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects
- Plasma and CSF amyloid, and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild to moderate AD subjects
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and, 18 months in MCI/Prodromal and mild to moderate AD subjects as measured by vMRI
- Brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- The population PK parameters of E2609 including the effect of intrinsic and extrinsic factors (including *NAT2* phenotype) in MCI/Prodromal and mild to moderate AD subjects

**Analysis Sets**

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set is the subset of subjects in the FAS who sufficiently comply with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

**Efficacy Analyses**

***The MCI/Prodromal cohort:*** This study in the MCI/Prodromal cohort is based on Bayesian adaptive design. Frequent interim analyses will be performed to assess the probability of early success and futility and to make early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis. Key definitions relevant to the Bayesian aspects of the adaptive design are given below.

**Study Definitions**

- **Maximum Effective Dose ($d_{Max}$):** The dose that achieves the greatest treatment effect.
- **$ED_{90}$:** The lowest dose that achieves at least 90% of the $d_{Max}$ treatment effect in the derived ADCOMS.
- **Early Success:** The study in the MCI/Prodromal cohort will meet early success criteria if the probability that the $ED_{90}$ at 18 months of treatment achieves 25% improvement over placebo is at least 80%. Early success is achieved before all MCI/Prodromal subjects complete 18 months of treatment and can only be determined after at least 200 MCI/Prodromal subjects have been randomized. If early success is declared before full randomization, the

randomization of new MCI/Prodromal subjects will stop but subjects already randomized into the study will receive the full 18 months of treatment (following confirmation from the Sponsor's Senior Management).

- **Futility:** The study in the MCI/Prodromal cohort will meet statistical futility criteria if the probability that the $ED_{90}$ is better than placebo by the clinically significant difference of 25% is less than 5% at 18 months of treatment. The statistical futility boundary is binding; if the statistical futility boundary is crossed the study will be considered to have failed.
- **Study Success:** The study in the MCI/Prodromal cohort will be considered a success if an $ED_{90}$ at 18 months treatment has at least an 80% probability of achieving 25% improvement over placebo at either an interim analysis or at the final analysis.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)***:*** All mild to moderate AD subjects will be included in the efficacy evaluations of the Mild to Moderate AD cohort. The analysis of the Mild to Moderate AD cohort is based on the group sequential design. Interim analyses in the Mild to Moderate AD cohort will only be performed after the MCI/Prodromal cohort crosses the early success boundary. The early efficacy signal based on the change from baseline of ADCOMS at 18 months is defined as crossing the interim-analysis boundaries for overwhelming efficacy in the mild to moderate AD population. The O'Brien-Fleming (OF) boundaries based on Lan-DeMets alpha spending function will be used to assess overwhelming efficacy. The corresponding OF boundaries based on *P* values will be 0.076, 0.0221, and 0.0423 for the first, second, and final analyses, respectively, according to 2 planned interim analyses at the 60% and 80% information fraction. (revised per Amendment 01)

**Analysis for the primary endpoint**

***Primary analysis of primary endpoint***

The primary analysis will be based on MCI/Prodromal subjects from the FAS with the prespecified censoring rule applied. The primary endpoint is the change from baseline to 18 months in the derived ADCOMS. The dose-response of the primary endpoint is modelled with a first-order normal dynamic linear model, where Normal and Inverse-Gamma priors are used. The primary efficacy analysis will calculate the Bayesian posterior probability that the dose identified is the most likely $ED_{90}$ dose that achieves 25% improvement over the placebo arm. At each interim analysis and the final analysis, 2 Bayesian probabilities will be summarized for each active dose: the probability it is the $ED_{90}$ dose and the probability of achieving 25% improvement over the placebo arm.

For the clinical efficacy data (ie, derived ADCOMS, MMSE, ADAS-cog, CDR, CBB, ISLT, and FAQ), subjects will be censored at the time of initiation of treatment with AChEIs or memantine, if they were not on these medications at the time of Baseline cognitive assessment (Visit 2), and will be censored at the time of dose adjustment of AChEIs or memantine if they were already on stable treatment with these medications at the time of Baseline cognitive assessment (Visit 2). The value of the primary endpoint for censored subjects will be imputed using data up to the censoring time and Bayesian longitudinal modeling.

***Sensitivity analyses of primary endpoint***

After unblinding, the primary endpoint will be analyzed using the Bayesian methods described above as well as conventional statistical methods. The following additional Bayesian analyses will be conducted as sensitivity analyses:

- The primary endpoint will be analyzed regardless of initiation of treatment, or dose adjustment, with AChEIs or memantine using the same Bayesian analysis method as primary analysis. This is an intent-to-treat analysis without any censoring.

- In case of early success, the primary analysis as well as the above sensitivity analyses will be repeated after all subjects have completed 18 months of treatment or have been lost to follow-up.

Statistical methods for the final conventional analyses will use a mixed-effects model with repeated measures (MMRM) on the change from baseline in the derived ADCOMS at 18 months. The model will include treatment groups, randomization stratification variables (the presence or absence of ongoing treatment with AChEIs or memantine or both, and *ApoE4* status), and baseline ADCOMS as covariates. Other covariates such as adjusted hippocampal volume will be studied. These analyses will be performed as sensitivity analyses on the FAS as well as the per protocol set, and as such, no multiplicity adjustments will be made to account for the interim analyses. In case of early success, the conventional analyses will also be performed using the data collected before the interim analysis.

**Analysis for the secondary endpoints**

***The MCI/Prodromal Cohort***

An MMRM will be used to analyze the following secondary endpoint: (revised per Amendment 02)

- Change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI

Comparisons between each treatment group and placebo will be performed.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

An MMRM will be used to analyze the change from baseline of derived ADCOMS at 18 months in mild to moderate AD. If there is no treatment group-by-population interaction in the overall study, the MMRM analysis will include all subjects (MCI/Prodromal or mild to moderate AD) in the overall study. Otherwise, the MMRM analysis will only include subjects in the Mild to Moderate AD cohort. The comparison between placebo and active doses will be performed within mild to moderate AD subjects regardless of subjects included in the MMRM analysis. Dunnett's method will be used to control for multiplicity due to multiple comparisons.

**Analysis for exploratory endpoints**

(revised per Amendments 01 and 02)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in the derived ADCOMS at 12 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in total hippocampal atrophy at 12 and 18 months in mild to moderate AD subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) after 4 weeks and 18 months in MCI/Prodromal and mild to moderate AD subjects. Data from early discontinuations will also be included. (revised per Amendment 02)
- Change from baseline in the clinical assessments: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in plasma and CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months as measured by vMRI in MCI/Prodromal and mild to

moderate AD subjects

A linear mixed-model will be used to analyze the following exploratory endpoints:

- Change from baseline in brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in CSF biomarkers of neurodegeneration (eg, tau, p-tau) at 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects

Data from early discontinuations will also be used as appropriate. Comparisons between each treatment group and placebo will be performed.

A linear mixed-model with repeated measures will be used to determine the relationship between the following endpoints:

- Change from baseline in the derived ADCOMS score and the change from baseline in biomarkers in CSF at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in the derived ADCOMS score and change from baseline in imaging biomarkers (hippocampal, whole brain, and total ventricular volumes) at 12 and 18 months in MCI/Prodromal and mild to moderate AD subjects

*ApoE* status for heterozygous and homozygous E4 carriers will be included in the model to assess the effect of *ApoE* status in this relationship.

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). CSF Aβ(1-x), Aβ(1-42), t-tau, p-tau, and BACE1 will be assessed and data will be presented graphically. Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status. Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels and exposure to E2609 in plasma and CSF will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. Additionally, the relationship between CSF exposure to E2609 and the derived ADCOMS at 18 months, and the relationship between CSF exposure to E2609 and the change from baseline for 18 months in the ADAS-cog, the CDR, and the

MMSE will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling.

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. Further information is in the "Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments" section. Details of pharmacogenomic testing may be provided and reported separately.

**Safety Analyses**

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, and vital sign measurements will be summarized

by treatment group using descriptive statistics.

Lymphocyte Subsets

Lymphocyte subsets (ie, CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages]) and regulatory T cells will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose. Serum IgG, IgM, IgA will be measured and summarized in the same manner as other laboratory parameters.

**Interim Analyses**

In order to make decisions about the remainder of the study as well as the full E2609 clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. Investigators, other clinical site staff, subjects and caregivers/informants will remain blinded to study treatment. (revised per Amendment 03)

An interim safety analysis will also be conducted when the first 60 subjects have completed 12 weeks of treatment (or discontinue study drug early) in Stage A. (revised per Amendments 01 and 03)

***The MCI/Prodromal Cohort***

Oversight of the Bayesian interim analyses and response adaptive randomization will be conducted by an independent committee that has expertise with Bayesian adaptive design in clinical studies. An unblinded external independent analysis group will provide the interim analysis outcomes to the committee at each interim analysis. The committee will ensure the integrity of the interim analysis and response adaptive randomization process through review of efficacy data. In addition, the committee will act in an independent advisory capacity to monitor the Bayesian interim analysis outcomes according to the early success and futility boundaries prespecified in the protocol. The committee will not be charged with any subject safety issues; this will remain the responsibility of the DSMB. The DSMB will continue to monitor the safety aspects of the study throughout Stage A and Stage B. The study may be stopped for safety at any time.

The first Bayesian adaptive interim analysis will be conducted when 100 MCI/Prodromal subjects have been randomized into the study (ie, including MCI/Prodromal subjects from both Stage A and Stage B). (revised per Amendment 01) Further interim efficacy analyses will be conducted after each additional 50 MCI/Prodromal subjects have been randomized, up to a maximum of 500 MCI/Prodromal subjects (ie, at 100, 150, 200, 250, 300, 350, 400, 450, 500 subjects randomized). If the study reaches full randomization, additional interim analyses will be conducted every 3 months until all subjects complete 18 months of treatment. The study will be monitored for futility at each interim analysis. Starting at the 200 subjects' interim analysis, the study will be monitored for success at each interim analysis. Each interim analysis will be conducted on data for the derived ADCOMS.

If the predefined early success criteria are met during the recruitment period, further recruitment and enrollment of MCI/Prodromal subjects into the study will stop (following confirmation from the Sponsor's Senior Management) and all currently randomized subjects will complete the full 18 months of treatment. No further interim analyses will be conducted after achieving early success.

If the predefined threshold for futility is reached, no additional subjects will be randomized into the study and the treatment of subjects already randomized into the study will stop and the study will be declared as "failed". All subjects will be monitored for safety for 3 months following their last dose.

If neither early success nor futility is reached and the study reaches full randomization, all subjects will complete 18 months of treatment. Interim efficacy analyses will be conducted every 3 months

after full randomization is reached to assess futility and early success until all subjects complete 18 months of treatment. After full randomization, all study subjects will stop treatment only in the event of futility.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

A group sequential design will be used for the Mild to Moderate AD cohort. This design includes 3 looks, 2 interim looks (when 60% and 80% information fractions are achieved) and 1 final look. Interim analyses will be performed after the MCI/Prodromal cohort crosses the early success boundary. The corresponding efficacy boundaries will be 0.076, 0.022, and 0.0423 for the first, second, and final analyses, respectively. If the actual information fraction during the interim analyses is different from 60% or 80% at the interim, the efficacy boundaries will be adjusted based on the actual information fraction. If early success in the MCI/Prodromal cohort is not achieved before the final analysis that is performed when all subjects have completed 18 months treatment, then only a final analysis will be performed in mild to moderate AD subjects. In the event of futility in the MCI/Prodromal cohort, an analysis will be performed for the Mild to Moderate AD cohort based on the data for mild to moderate AD subjects available at that time. (revised per Amendment 01)

**Adaptive Randomization in the MCI/Prodromal Cohort**

Randomization to placebo or 1 of 3 dose groups of E2609 will be fixed for the first 100 MCI/Prodromal subjects randomized in the study (1:1:1:1; placebo to each of the 3 active doses for the first 100 MCI/Prodromal subjects randomized, including those randomized from both Stage A and Stage B). Thereafter, randomization probabilities to each treatment group will be updated at each interim analysis, such that the randomization probability will be increased for the placebo group and dosage groups that represent the potential target dose ($ED_{90}$), and simultaneously decreased for other active arms. (revised per Amendment 01)

**Randomization in the Mild to Moderate AD Cohort** (revised per Amendment 01)

In Stage A, the mild to moderate AD subjects will be randomized to placebo or 1 of 3 E2609 dose groups (5, 15, and 50 mg of E2609) at a 1:1:1:1 ratio, while in Stage B, the mild to moderate AD subjects will be randomized to placebo or 1 of 2 E2609 dose groups (15 and 50 mg E2609) at a 1:1:1 ratio. (revised per Amendment 01)

**Stratification** (revised per Amendment 01)

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

**Sample Size Rationale**

***Sample Size Rationale in the MCI/Prodromal cohort***

Primary endpoint – derived ADCOMS: The sample size and design characteristics to test the hypothesis for the primary objective based on the primary endpoint were determined by means of simulations. Extensive study simulations have shown that a total of 500 subjects will be sufficient to demonstrate that the most likely $ED_{90}$ dose achieves a 25% improvement over placebo with a probability of at least 80% in the interim and final analyses. There is at least a 90% probability of study success for the dose response scenarios where treatment was considered to have a clinically meaningful treatment effect. Simulations have also shown that if there is no obvious dose effect, the probability of falsely claiming superiority to placebo is at most 5%.

For each of the 4 treatment groups (3 active doses and placebo), the final number of subjects per

group will differ depending on the observed interim treatment responses.

vMRI: The null hypothesis is that there is no difference between active dose and placebo. There are 3 null hypotheses corresponding to 3 active doses. The alternative hypothesis is that at least 1 null hypothesis is false (1-sided). The null hypotheses will be tested using Dunnett's method with 1-sided alpha of 0.05. The statistical power was estimated through simulation for a moderate dose-response assumption that the percent reduction in change from baseline of total hippocampal volume compared with placebo would be 15%, 20%, and 25% corresponding to the 3 doses, respectively. The estimated power for actual planned study sample size is 78% at 18 months assuming an attrition rate of 20% at 18 months. Under a stronger dose-response assumption (ie, the percent reduction in change from baseline of total hippocampal volume compared with placebo is twice as much as that in the moderate dose-response assumption), the estimated power is at least 99% at 18 months.

Amyloid PET: The null and alternative hypotheses and statistical test are the same as those for vMRI. To estimate the sample size for the amyloid PET imaging subgroup at 18 months, a common SD of change from baseline was estimated at 0.33 and a reasonable mean difference between treatment and placebo was estimated as 0.25 (standardized uptake value ratio [SUVR]). Assuming a moderate dose-response, the best dose would achieve a difference of 0.25 (SUVR) and the middle and low doses would achieve a difference of 0.2 and 0.15 (SUVR), respectively, it would require a total of 100 subjects from all 4 arms at 18 months to achieve 80% power.

***Sample Size Rationale for the Mild to Moderate AD Cohort*** (revised per Amendment 01)

ADCOMS at Month 18: The null hypothesis is that there is no difference between active dose and placebo. There are 2 null hypotheses corresponding to 2 active doses. The alternative hypothesis is that at least 1 null hypothesis is false. The null hypotheses will be tested using Dunnett's test with 2-sided alpha of 0.05 as described for the Mild to Moderate AD cohort in the secondary analysis section. The statistical power was estimated through simulation for the dose-response assumption that the percent reduction in change from baseline of ADCOMS at 18 months compared with placebo would be 33% and 50% corresponding to the 2 doses, respectively. The estimated power for the actual planned 200 mild to moderate AD subjects is approximately 80% assuming a 2-sided alpha of 0.05. (revised per Amendment 01)

# 3 TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES



## LIST OF IN-TEXT FIGURES



## LIST OF APPENDICES

# 4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| Aβ | amyloid β |
| Aβ(1-x) | amyloid β (1-x) (ie, the amyloid β monomer from amino acid 1 to x [eg 1-42]) |
| AChEI | Acetylcholinesterase inhibitor |
| AD | Alzheimer's disease |
| ADAS-cog | Alzheimer's Disease Assessment Scale - cognitive subscale |
| ADCOMS | Alzheimer's Disease Composite Score |
| AE | Adverse Event |
| ApoE | Apolipoprotein E |
| AUC | area under the concentration x time curve |
| $AUC_{(0\text{-}24h)ss}$ | area under the concentration x time curve at steady state from time zero to 24 hours |
| BACE1 | Beta-amyloid converting enzyme 1 |
| BP | blood pressure |
| bpm | beats per minute |
| CBB | CogState Brief Battery |
| CBC | complete blood count |
| CBP | childbearing potential |
| CDR | Clinical Dementia Rating |
| CES2 | carobxyesterase-2 |
| CFR | Code of Federal Regulations |
| $C_{max,ss}$ | maximum plasma concentration at steady state |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| CRA | clinical research associate |
| CRF | case report form |
| CRO | contract research organization |
| CSF | cerebrospinal fluid |
| $C_{ss,av}$ | average steady-state concentration |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CTA | Clinical Trial Agreement |
| CYP | cytochrome P450 |
| $d_{Max}$ | Maximum effective dose |
| DSMB | data safety monitoring board |
| ECG | electrocardiogram |

| Abbreviation | Term |
|---|---|
| eCRF | electronic case report form |
| ED | early discontinuation |
| $ED_{90}$ | lowest effective dose that achieves 90% of the greatest treatment effect |
| ELISA | enzyme-linked immunosorbent assay |
| FAQ | Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire) |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FLAIR | fluid-attenuated inversion recovery |
| GCP | Good Clinical Practice |
| GDS | Geriatric Depression Scale |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |
| HCVAb | hepatitis C virus antibody |
| HSV | herpes simplex virus |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ID | identifier |
| IEC | Independent Ethics Committee |
| Ig | immunoglobulin (eg, IgA, IgG, IgM) |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISLT | International Shopping List Task |
| IxRS | interactive voice and web response system |
| LLN | lower limit of normal |
| LNH | low/normal/high |
| LP | lumbar puncture |
| MAD | multiple ascending dose |
| MCI | mild cognitive impairment |
| MCI/Prodromal | Mild Cognitive Impairment due to Alzheimer's Disease/ Prodromal Alzheimer's Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mild to moderate AD | mild to moderate dementia due to Alzheimer's Disease |
| miRNA | micro-ribonucleic acid |
| MMRM | mixed-effects model with repeated measures |

| Abbreviation | Term |
|---|---|
| MMSE | Mini Mental State Examination |
| MRI | magnetic resonance imaging |
| NAT2 | N-acetyltransferase 2 |
| NIA-AA | National Institute on Aging-Alzheimer's Association |
| OF | O'Brien-Fleming |
| PBMC | peripheral blood mononuclear cell |
| PD | Pharmacodynamic(s) |
| PET | positron emission tomography |
| PGx | pharmacogenomic(s) |
| PK | pharmacokinetic(s) |
| PP | per protocol |
| PRN | Pro re nata |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| p-tau | phosphorylated-tau |
| QD | once daily |
| QTc | corrected QT interval |
| QTcF | QTc interval calculated using Fridericia's formula |
| R | randomization |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reaction |
| SUVR | standardized uptake value ratio |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |
| TEMAV | treatment-emergent markedly abnormal laboratory values |
| t-tau | total tau |
| ULN | upper limit of normal |
| UNS | unscheduled |
| vMRI | volumetric magnetic resonance imaging |
| WHO DD | World Health Organization Drug Dictionary |
| β-hCG | beta-human chorionic gonadotropin |

# 5 ETHICS

## 5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA][s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigators or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

## 5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (CFR) (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

- European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved European Union member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

## 5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject and the identified caregiver or informant, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or understand it or if the identified caregiver or informant is unable to read, an impartial witness should be present during the entire informed consent discussion. If, in the Investigator's opinion, a subject lacks capacity to consent, the subject's assent should be obtained in addition to the written informed consent of a legal representative (capacity to consent and definition of legal representative should be determined in accordance with applicable local laws and regulations). (revised per Amendment 01) After the ICF and any other written information to be provided to subjects is read and explained to the subject and the identified caregiver or informant, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified caregiver or informant should also consent to supporting the subject's participation in the study and will be provided with a separate written ICF for his or her participation in the study, to be signed before he or she participates in any further aspects of the study.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified caregiver or informant must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified caregiver or informant will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified caregiver or informant should be

informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

All subjects will also be asked to provide written consent for cerebrospinal fluid (CSF) sampling at Baseline and after receiving study drug for 4 weeks and 18 months (or at Early Discontinuation). This consent for CSF sample collection is not required for study eligibility. (revised per Amendment 02)

# 6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 125 investigational sites globally (40 sites in the United States for Stage A and 125 sites globally for Stage B). (revised per Amendments 01 and 02)

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

# 7 INTRODUCTION

At this time, there is no cure for Alzheimer's disease (AD), no known way of slowing down the progression of this disease, and no approved treatment available to reverse the deterioration. There is, therefore, an urgent unmet medical need for drugs that slow or prevent disease progression. Beta-amyloid converting enzyme 1 (BACE1) is a key enzyme responsible for the production of amyloid β (Aβ) peptides and plaque formation, and several reports have described elevated levels of BACE1 in AD brains (Coulson, et al., 2010, Lu, et al., 2012). Once amyloid plaques form, Aβ causes BACE1 levels to increase further, thus accelerating Aβ generation and plaque growth via a positive feedback loop. Therefore, BACE1 is a promising target for modifying or treating AD.

It is now widely accepted that mild cognitive impairment (MCI) due to AD and mild to moderate AD dementia are stages on a single disease spectrum, which follows an Alzheimer's pathological cascade. (revised per Amendment 01) Recent consensus papers from the international workgroups of the National Institute on Aging-Alzheimer's Association (NIA-AA), have endorsed this hypothesis (Albert, et al., 2011; Jack, et al., 2011; McKhann, et al., 2011; Sperling, et al., 2011).

From a clinical standpoint, demonstration of an effect on slowing disease course is hampered by the lack of sensitive tools for detecting relatively small changes in progression or treatment effect especially in early disease. In addition, drugs that are expected to slow disease progression require longer study durations to ensure adequate separation from placebo. These challenges have resulted in the use of biomarkers as surrogates for clinical effect in Phase 2 studies, in order to facilitate the development process for disease modifying agents. However, subsequent Phase 3 AD studies based solely on biomarker findings in Phase 2 have failed to show clinical effect, due, in part, to the fact that biomarkers may not predict clinical outcomes for potential disease modifying agents. These findings underscore the need for innovative approaches to clinical study design for measuring the effect of treatment.

E2609 is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, E2609 inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in cerebrospinal fluid (CSF) and plasma (rat, guinea pig, and monkey). In humans, E2609 has been shown to inhibit BACE1 enzyme activity in CSF and lower the levels of Aβ, including amyloid beta monomer from amino acid 1 to x (Aβ[1-x]), Aβ(1-40) and Aβ(1-42), in CSF both in vitro and in vivo. See the Investigator's Brochure for additional information. The target indication for E2609 is therefore treatment and disease modification of AD.

The present clinical study represents the sole Phase 2 study for the E2609 program, and is designed to establish Proof of Concept in subjects with Mild Cognitive Impairment due to Alzheimer's Disease/Prodromal Alzheimer's Disease (referred to as MCI/Prodromal throughout the protocol). The study also allows investigation of efficacy in subjects with mild to moderate dementia due to Alzheimer's Disease (referred to as mild to moderate AD throughout the protocol) to determine whether the effects of E2609 in this later stage population are comparable with those established in the MCI/Prodromal population within

this same study. (revised per Amendment 01) In the MCI/Prodromal population, Bayesian response adaptive randomization design is used with frequent interim analyses to continually update randomization allocation based on emerging clinical endpoint data. This approach allows for ongoing assessment of drug futility or evidence of early success and can mitigate the risks associated with larger and longer studies required to demonstrate clinical efficacy by leading to more efficient study termination or early advancement to a Phase 3 program. Results from this study will guide both the decision to move into Phase 3 development and the selection of the dose strengths to be taken into Phase 3. Moreover, this study is intended to be supportive for registration in the MCI/Prodromal population.

In the MCI/Prodromal population, this study will compare placebo and 3 oral doses of E2609 (5, 15, and 50 mg) administered once daily (QD) for 18 months. In the mild to moderate AD population, this study will compare placebo and 2 oral doses of E2609 (15 and 50 mg) administered QD for 18 months. To date, the longest duration of dosing with E2609 is 14 days (multiple ascending dose [MAD] Study E2609-A001-002 [Study 002]). (revised per Amendment 01)

This study (E2609-G000-202 [Study 202]) will comprise 2 stages: Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 in the United States sites only, before expanding enrollment to a larger and more global population of subjects in Stage B. This design will allow close monitoring of safety by an independent data safety monitoring board (DSMB), including a formal safety review as soon as the first 60 randomized subjects have completed 12 weeks of treatment, have discontinued study drug or have withdrawn from the study. The study also includes a number of exclusion criteria, specific blinded safety monitoring procedures and safety criteria for discontinuation of study drug in light of the preclinical and clinical safety data collected to date following administration of E2609.

## 7.1 Nonclinical and Clinical Safety Data

The toxicity of E2609 has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomologus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by E2609 in a clinical setting. Further details of the nonclinical data to date with E2609 can be found in the Investigator's Brochure.

The clinical program to date includes 6 Phase 1 studies:

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, single ascending dose (SAD) study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50-mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled MAD study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the pharmacokinetic (PK) levels of E2609 and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of E2609. It also investigated the effects of E2609 on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [$^{14}$C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of E2609 under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) was a randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with E2609. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with E2609. In elderly subjects treated with 50 mg of E2609, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTc interval calculated using Fridericia's formula (QTcF) from baseline (14.9 msec at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of E2609 might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that E2609 altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of E2609. A single dose of E2609 up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, E2609 administered at doses of 200 and 400 mg was associated with

reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of E2609 on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP3A4] and carboxyesterase-2 [CES2]) increased by approximately 70% the area under the concentration × time curve (AUC) of E2609. Consequently, strong inhibitors of CY3A4 will be prohibited in this study.

Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of E2609. Therefore, no restrictions are required for the use of concomitant medications which are known to be inducers of CYP450 enzymes. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of E2609 when coadministered with E2609 but not when dosed at least 2 hours apart from E2609. E2609 (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of E2609. Therefore, on the basis of drug interaction considerations, the only restriction of concomitant medications is that for strong inhibitors of CYP3A4.

# 8 STUDY OBJECTIVES

## 8.1 Primary Objectives

The primary objectives are:

1. To evaluate the efficacy of daily dosing with 3 doses of E2609 compared with placebo by establishing the lowest effective dose that achieves 90% of the greatest treatment effect ($ED_{90}$) for E2609 on the derived Alzheimer's Disease Composite Score (ADCOMS) at 18 months of treatment in subjects with MCI/Prodromal
2. To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with mild to moderate AD (revised per Amendment 01)

## 8.2 Secondary Objectives

The secondary objectives are: (revised per Amendment 02)

1. To evaluate the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects, as measured by volumetric magnetic resonance imaging (vMRI)
2. To evaluate the efficacy of E2609 compared with placebo on the derived ADCOMS at 18 months in mild to moderate AD subjects (revised per Amendment 01)

## 8.3 Exploratory Objectives

(revised per Amendments 01 and 02)

The exploratory objectives are:

1. To explore the effect of E2609 compared with placebo on the derived ADCOMS following 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
2. To explore the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in mild to moderate AD subjects, as measured by vMRI
3. To explore the effects of E2609 compared with placebo on Aβ(1-x) and Aβ (1-42) in CSF after 4 weeks and 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects (revised per Amendment 02)

4. To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during posttreatment follow-up, in MCI/Prodromal and mild to moderate AD subjects, by assessment of:
   a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
   b. The Clinical Dementia Rating (CDR) scale
   c. The Mini-Mental State Examination (MMSE)
   d. The CogState Brief Battery (CBB)
   e. The Functional Assessment Questionnaire (FAQ; (also known as the Functional Activities Questionnaire)
   f. The International Shopping List Task (ISLT)
5. To explore the effects of E2609 compared with placebo on various biomarkers in MCI/Prodromal and mild to moderate AD subjects. Biomarkers to be explored include:
   a. CSF biomarkers of neurodegeneration (eg, tau, phosphorylated-tau [p-tau]) after 18 months of treatment
   b. Plasma and CSF amyloid, and CSF BACE1 measurements during 18 months of treatment and during posttreatment follow-up
   c. vMRI measurements including left and right hippocampal volume, whole brain volume, and total ventricular volume at 6, 12, and 18 months of treatment and during posttreatment follow-up
   d. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)
6. To characterize the population PK of E2609 in MCI/Prodromal and mild to moderate AD subjects, and to examine the effect of intrinsic and extrinsic factors (including N-acetyltransferase 2 [*NAT2*] phenotype) on the PK
7. To explore the relationship between the treatment effects of E2609 on the ADCOMS and its effects on CSF amyloid, CSF BACE1, CSF tau, and vMRI in MCI/Prodromal and mild to moderate AD subjects

# 9 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan

Study 202 is a multicenter placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild to moderate AD. (revised per Amendment 01)

A common set of inclusion criteria, consistent with the NIA-AA clinical research criteria for MCI due to AD or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study will be conducted in 2 stages, Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 (at least 12 weeks) before expanding enrollment to include a larger number of subjects in Stage B. All MCI/Prodromal subjects will be included in the primary efficacy evaluation irrespective of whether they were recruited into Stage A or Stage B. Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B. All mild to moderate AD subjects will be included in the efficacy evaluation of that cohort. (revised per Amendment 01)

Both Stage A and Stage B will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days, plus an additional window of up to 30 days if required [revised per Amendment 02]) will consist of a Screening Visit and a Baseline Visit. Screening assessments will be organized into 4 tiers; see Section 9.5.2.2, Table 6, and Figure 2.

All screening assessments must be completed, and eligibility to continue to the Baseline Period confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

In Stage A, all subjects (MCI/Prodromal and mild to moderate AD) will be randomized 1:1:1:1 to 4 treatment groups (E2609 at 3 doses or placebo). In Stage B, randomization of MCI/Prodromal subjects will start off at a 1:1:1:1 ratio (E2609 at 3 doses or placebo), until a total of 100 MCI/Prodromal subjects have been randomized. Remaining subjects in the MCI/Prodromal cohort will be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. Subjects with mild to moderate AD who are recruited in Stage B will be randomized in a 1:1:1 ratio to 3 treatment groups (E2609 at 2 doses or placebo). (revised per Amendment 01)

An overview of the study design is presented in Figure 1 .

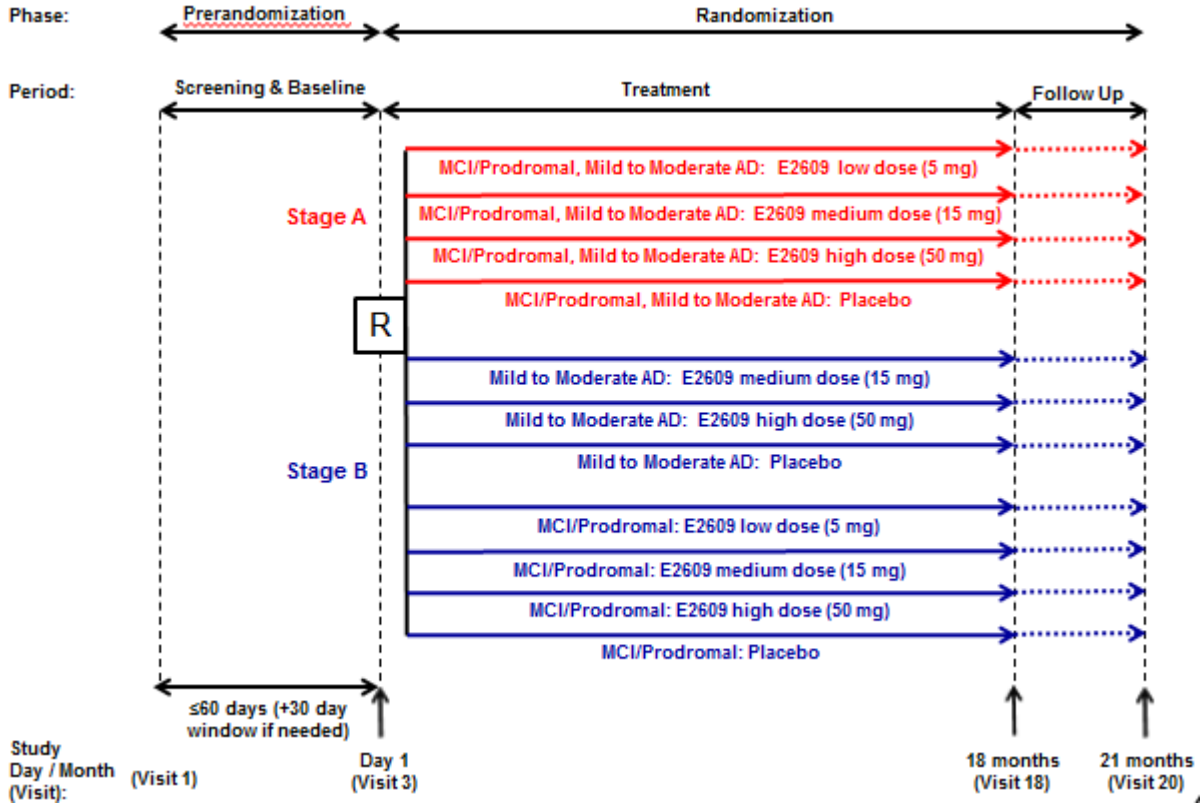



**Figure 1 Design of Study E2609-G000-202**

**(revised per Amendments 01 and 02 )**

R = randomization.

### Stage A

Stage A will be limited to approximately 40 sites in the United States. (revised per Amendments 01 and 02) Stage A will randomize 60 eligible subjects at Visit 3, 1:1:1:1 to 4 treatment groups within each clinical cohort. (revised per Amendment 01) There will be no Bayesian adaptation during Stage A. In addition to the placebo group, 3 doses of E2609 will be used to reduce CSF Aβ levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/PD modeling shows these doses should achieve these targets when administered QD with food and will be evaluated based on the 4-week assessment of CSF Aβ(1-x) from subjects who provide voluntary consent for CSF measurement. (revised per Amendment 02) (see Section 9.4.4).

During Stage A, safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the first subject is randomized during Stage A, an independent DSMB (including at least 1 immunologist) will review all safety data in an unblinded manner. The DSMB will make recommendations to Eisai after each

review as to whether any change(s) to the study are necessary. Unless the DSMB recommends otherwise, randomization of subjects into Stage A will continue until 60 subjects have been randomized and dosed. (revised per Amendment 01)

Interim analyses of the E2609 PK and PD profiles will be performed on subjects who consent to provide CSF samples at Baseline and after 4 weeks of study drug. These interim analyses, as well as analyses of safety data, will be performed on an ongoing basis throughout Stage A. Refer to Section 9.7.3 for more detail. (revised per Amendment 03) These data will be used to evaluate the CSF PD effects of E2609 doses, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels (see Section 9.4.4). (revised per Amendments 01 and 02) The mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment for each dose of E2609 and its 90% confidence interval will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data from Stage A and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline after 4 weeks of dosing. (revised per Amendment 02)

Once 60 subjects in Stage A have completed at least 12 weeks of treatment (or discontinued study drug early) an interim safety analysis will be conducted by Eisai and the DSMB. (revised per Amendment 01) Subjects in Stage A will continue study drug while the DSMB reviews all the available safety data, but randomization of additional subjects will not take place (ie, recruitment into Stage B will not commence) until the safety analysis is completed by the DSMB. At the time of this interim safety analysis, some subjects will have more than 12 weeks of safety data.

If there are safety signals with one of the E2609 dose groups that would require dose adjustment, changes to dose will be reflected in an amendment to the protocol. Information on how these subjects will be handled in the primary analysis will be described in the Statistical Analysis Plan.

**Stage B**

Stage B will start after the DSMB safety review of Stage A has shown acceptable safety and tolerability of E2609 and after the doses of E2609 to be used in Stage B are evaluated. (revised per Amendment 02) Based on data from Stage A, the protocol will be reviewed and may be amended before beginning Stage B. Safety data from Stage B will continue to be reviewed by the DSMB (approximately every 3 months) until recruitment in the study is completed; following this the DSMB will meet approximately every 6 months.

Stage B will be conducted globally and will enroll, randomize, and dose additional eligible subjects up to a maximum of 500 MCI/Prodromal subjects and up to a maximum of 200 mild to moderate AD subjects. The final total number of MCI/Prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. (revised per Amendment 01)

In Stage B, both cohorts will include separate placebo groups. The MCI/Prodromal cohort will include 3 doses of E2609 (5, 15, and 50 mg QD), whereas the Mild to Moderate AD cohort will only include 2 doses of E2609 (15 and 50 mg QD). (revised per Amendment 01)

Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort during Stage B. Randomization of MCI/Prodromal subjects into Stage B will commence according to a fixed schedule (1:1:1:1; placebo:5 mg E2609:15 mg E2609:50 mg E2609) until a total of 100 MCI/Prodromal subjects (including those from Stage A) have been randomized. (revised per Amendment 01) The remaining subjects in the MCI/Prodromal cohort in Stage B will then be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. The mild to moderate AD subjects will be randomized according to a fixed schedule (1:1:1 placebo; 15 mg E2609; 50 mg E2609) throughout Stage B. (revised per Amendment 01)

Interim analyses are planned and are discussed in Section 9.7.3. (revised per Amendment 03)

### 9.1.1 Prerandomization Phase

The Prerandomization Phase includes a Screening Visit and a Baseline Visit. All Screening Visit assessments must be completed and eligibility to progress must be confirmed before any Baseline Visit assessments are performed. All Screening Visit and Baseline Visit assessments must be completed within 50 days (plus an additional window of up to 30 days if required [revised per Amendment 02]) and a window of no more than 10 days is to be observed between the completion of all Baseline Visit assessments (including confirmation of eligibility following all Baseline Visit assessments) and randomization into the study at Visit 3 (revised per Amendment 02). Thus, the Prerandomization Phase will last for up to 60 days, plus an additional window of 30 days if required (revised per Amendment 02). The series of assessments conducted during this phase will determine eligibility for randomization into the study.

Inclusion criteria are discussed in Section 9.1 and detailed in Section 9.3.1. Before randomization the clinician will provide a judgment on the classification of a subject as either MCI/Prodromal or likely mild to moderate AD. (revised per Amendment 01) This judgment may be discussed and reviewed with the Sponsor or Sponsor's representative, as necessary.

Results of the Screening safety magnetic resonance imaging (MRI) will be valid for 90 days from the date of scanning. Results of the lumbar puncture (LP) from subjects who voluntarily consent for CSF measurement will be valid for 90 days from the date of testing. Results of Screening PET scans conducted specifically for this study and for use in the longitudinal analyses will also be valid for 90 days from the date of scanning. These assessments will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. Historical PET scans used for determination of eligibility only (ie, not used for the longitudinal analyses) are valid for 12 months. (revised per Amendment 02)

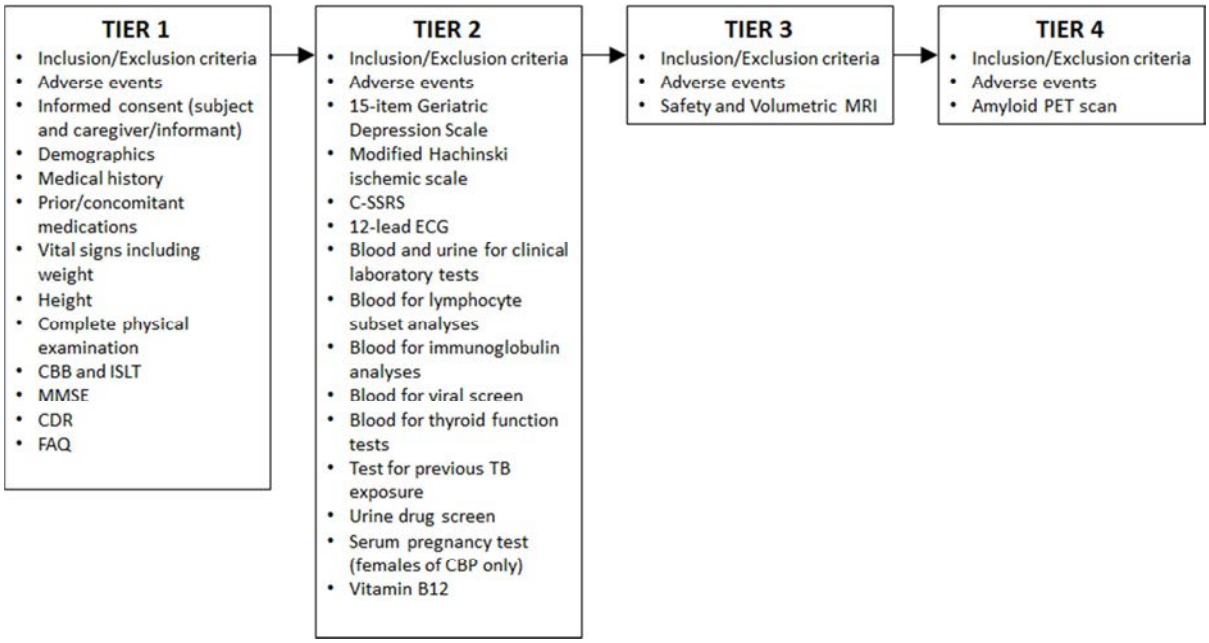
#### 9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and caregiver or informant, and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained from both the subject and the caregiver or informant. The caregiver or informant needs to be present at this visit.

Study site personnel will interview the subject and caregiver or informant to obtain demographic and clinical information as described in Table 6, and will review inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2 and perform any required assessments in order to complete these criteria. Prior medications and medications currently being taken by the subject will be reviewed (see Section 9.4.7). The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

Clinical assessments for eligibility will be conducted during the Screening Visit as described in Table 6 and Figure 2.

Every effort should be made to conduct these assessments in the morning, but if this is not possible, they should be conducted at the same time of day at all subsequent visits. The screening assessments/procedures have been organized into 4 distinct tiers (Table 6 and Figure 2). All assessments/procedures in each tier should be completed, and eligibility to continue screening in the study confirmed, before any assessments/procedures from the next tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures as long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. (revised per Amendment 01)




## Figure 2 Assessments to be Performed at Screening by Tier

CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), ISLT = International Shopping List Task (immediate and delayed recall), MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PET = positron emission tomography, TB = tuberculosis.

Cognitive assessments (Tier 1) are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). The recommended order of assessments at Screening is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. (revised per Amendment 02) The investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session (Tier 3).

Amyloid PET imaging will be used to confirm all subjects have amyloid deposition in the brain (Tier 4). An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. If an historical amyloid positive PET scan is being used, it should be submitted to the central PET reading group after the subject has completed and passed all Tier 1 assessments. (revised per Amendment 02)

#### 9.1.1.2 Baseline Period

All Screening Visit assessments must be completed (and eligibility to progress confirmed) before any Baseline Visit assessments are performed. The Baseline Visit assessments (per Table 6 and Section 9.5.1.2) are to be completed as soon as possible after completion of the final Screening Visit assessment (ie, PET scan) such that all Screening Visit and Baseline Visit assessments are completed within 50 days, plus an additional window of up to 30 days if required. (revised per Amendment 02)

Inclusion and exclusion criteria will again be reviewed, vital signs including weight will be recorded, and a 12-lead ECG will be conducted in triplicate. A routine physical examination will be conducted and a dermatological assessment and neurological examination will be performed. A urine pregnancy test will be conducted for females of childbearing potential. Blood will be collected from all subjects for clinical chemistry and hematology, lymphocyte subset analyses, Ig analyses, and PD assessments. Blood samples will be collected and stored for determination of a subject's previous exposure to infective pathogens in the event of AEs that warrant further investigation occurring at a later point in the study. Psychometric assessments will be administered to the subject in the order stated in Table 6. The caregiver or informant needs to be present at this visit. The Columbia Suicide Severity Rating Scale (C-SSRS) will also be administered (Section 9.5.1.5.11).

For subjects who consent to CSF sample collection, CSF will be obtained at this visit for PK and PD assessments (see Section 9.5.1.5.3). (revised per Amendment 02)

Blood will be collected from all subjects for pharmacogenomic (PGx) analyses of apolipoprotein E (*ApoE*) and the *NAT2* phenotype of subjects enrolled in the study (see Section 9.7.1.7.2).

### 9.1.2 Randomization Phase

Subjects who complete the Baseline Visit assessments, and are eligible based on the inclusion and exclusion criteria (see Section 9.3.1 and Section 9.3.2), will begin the Randomization Phase no more than 10 days after completion of the Baseline Visit assessments and confirmation of the eligibility of the subject based on the results of all the Baseline Visit assessments (revised per Amendment 02).

The Randomization Phase will consist of a Treatment Period of 78 weeks duration and a Follow-Up Period of 12 weeks after the last dose of study drug.

#### 9.1.2.1 Treatment Period

Subjects will be randomized at the beginning of the Treatment Period and will receive study drug or placebo, to be administered orally QD with food. Double-blinding to study drugs will be in effect throughout the Treatment Period. The dose for a subject will not be changed during the study. However, dose adjustment for Stage B may be considered and subjects already randomized to a dose that needs to be adjusted will be switched to continue their treatment at the new adjusted dose.

Safety criteria for discontinuation of study drug are detailed in Section 9.3.3.

Subjects will attend the study site every week for the first 4 weeks after beginning study drug, then fortnightly until 12 weeks have elapsed since first dose. Visits will then be conducted at 16, 20, 26, 39, 52, 65, and 78 weeks after the first dose.

#### 9.1.2.2 Early Discontinuation

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug.

Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie. at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB and ISLT) will be conducted. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) after the Early Discontinuation Visit or within ± 8 days of either of the Follow-Up Visits (Visit 19 and Visit 20). Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

#### 9.1.2.3 Follow-up Period

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug (Visit 19) and a second 12 weeks after the last dose of study drug (Visit 20). If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the posttreatment Follow-Up period.

The end of the study will be defined as the date of the clinical database lock (ie, when all study data are collected and data validation is completed).

As required by some regulatory agencies, the following estimates are provided:

- The study will begin in Nov 2014 and is projected to end by Oct 2019 (end date will depend on actual recruitment rate).
- The maximum estimated period for each subject on study is anticipated to be approximately 2 years.

## 9.2 Discussion of Study Design, Including Choice of Control Groups

### 9.2.1 Overview

The 2 stage design of the study allows for the safety and tolerability of E2609 to be assessed in a limited number of subjects (n=60) before expanding recruitment into a larger population of subjects. (revised per Amendment 01)

The design of this study allows Proof of Concept to be established in subjects with MCI/Prodromal AD. The study also allows investigation of efficacy in subjects with mild to moderate AD to determine whether the effects of E2609 in this later stage population are comparable with those established in the MCI/Prodromal population within this same study (see Section 9.2.3 for discussion of the Bayesian design used in this study). (revised per Amendment 01)

The inclusion criteria for the MCI/Prodromal cohort will be consistent with the NIA-AA criteria for MCI due to AD (Albert, et al., 2011) and with the definition of Prodromal AD per Dubois et al., 2010 (see Section 9.2.2).

There is no active or positive control for this study as at this time, there is no cure for AD, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary efficacy tool for this Proof of Concept study is the composite scale ADCOMS (change from baseline in the derived ADCOMS at 18 months). The ADCOMS (Hendrix, et al., 2012) represents a novel composite approach integrating components of well-established tools (ADAS-cog, MMSE, and CDR) to improve sensitivity to disease progression and treatment effects in subjects with AD (see Section 9.2.4).

Secondary efficacy endpoints include a biomarker of neuronal degeneration (shrinkage of neurons), which is the change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI; and a cognitive and functional assessment, which is the change from baseline in the derived ADCOMS at 18 months of treatment in mild to moderate AD subjects. (revised per Amendments 01 and 02) Exploratory endpoints including assessments of efficacy, safety and other biomarkers are also included.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

The rationale for the selection of doses used in the study is provided in Section 9.4.4.

### 9.2.2 Rationale for Study Population

By the time AD progresses to dementia, with loss of functional capabilities, the amyloid load in the brain is approaching a plateau and significant neurodegeneration has occurred (Jack, et al., 2010). Consequently, there is a growing view within the AD field that it may be necessary to initiate disease modifying treatments earlier, before the onset of clinical dementia (Aisen, et al., 2010). However, this hypothesis remains to be demonstrated with clinically effective therapies, and may not apply to all therapeutic classes, it is possible that this consideration explains the failure of the humanized monoclonal antibody bapineuzumab

(which targeted brain amyloid) to demonstrate clinical efficacy in late-phase studies in mild to moderate AD dementia. (revised per Amendment 01)

With this consideration taken into account, the primary clinical population of focus in this study is subjects with MCI/Prodromal AD. The mechanism of action of a BACE1 inhibitor where amyloid production is reduced means E2609 is more likely to be efficacious (ie, slow disease progression) the earlier in disease progression treatment is started, where limited neurodegeneration has occurred and associated clinical deficits are at a minimum. However, since the effect of BACE1 inhibition along the AD continuum remains to be characterized, E2609 will also be evaluated for its profile in mild to moderate stages of AD, in the event data emerge supporting its use beyond MCI/Prodromal AD. Indeed, recent data support the notion of continued progression of amyloid pathology even in these later stages of the disease (Hu, et al., 2015), although at a slower pace, suggesting a positive effect of BACE inhibition and amyloid beta reduction cannot be ruled out even in the later stages of the disease trajectory. Hence, in this study, E2609 will be assessed in subjects with disease states ranging from MCI/Prodromal to mild and even moderate AD. (revised per Amendment 01)

As discussed, efficacy is more likely to be observed in subjects with MCI/Prodromal AD but there is the possibility that efficacy will also be evident following administration of an amyloid modifying agents such as E2609 in subjects with more advanced disease such as mild to moderate AD. (revised per Amendment 01) For example, a study of tarenflurbil, a selective Aβ(1-42)-lowering agent, on cognition and function in subjects with mild to moderate AD showed the subjects with mild AD had lower rates of decline than those in the placebo group in activities of daily living and global function; however, slowing of cognitive decline did not differ significantly (Wilcock, et al., 2008). Similarly, differential effects on cognitive measures have been observed with solanezumab, where some benefit from treatment was observed in subjects with mild AD, although studies with solanezumab were considered to have failed to improve cognition or functional ability significantly (Doody, et al., 2014). Therefore, it is relevant to compare the effect of the BACE1 inhibitor E2609 in 2 different subject populations that differ in terms of AD severity before the initiation of large Phase 3 clinical studies. (revised per Amendment 01)

### 9.2.3 Rationale for the Use of Bayesian Adaptive Design

This study uses a Bayesian adaptive design for the MCI/Prodromal cohort only in Stage B. This design optimizes subject allocation and evaluation of efficacy in a smaller number of subjects by maximizing the number of subjects exposed to doses of interest. Frequent interim analyses will be performed to assess the probability of early success and futility and to aid in making early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis, such that subjects are more likely to receive a dose that is efficacious.

Subjects with mild to moderate AD will be assessed as a "nested" population that does not follow the Bayesian adaptive design. It was not considered appropriate to have a Bayesian design for both cohorts as this would have substantially increased the overall study sample size, delayed analyses of dose response, and would have added background "noise" for the

comparison of subjects with MCI/Prodromal AD compared with those with mild to moderate AD. Data from each cohort will be analyzed independently for the purposes of decision making. A separate analysis of the 2 cohorts avoids the risk of data from subjects with mild to moderate AD confounding the results for the primary population (MCI/prodromal). (revised per Amendment 01)

### 9.2.4 Rationale for Clinical Endpoints

The ADCOMS (Hendrix, et al., 2012) was developed utilizing data from multiple studies to investigate responsiveness to progression and treatment effects rather than sensitivity to baseline deficits. The score was built empirically with no a priori assumptions, using a partial least squares regression model for placebo data from 4 MCI studies with a duration ≥12 months. A combination of cognitive and functional items was selected from a variety of well-established and validated scales that is most sensitive to change over time. The partial least squares regression coefficients from the model were used to form a weighted composite score comprising a total of 12 individual items taken from the ADAS-cog (4 items), the MMSE (2 items), and CDR (6 items), that assess both cognition and global function. Performance of the ADCOMS has been assessed against the original scales in several studies. The use of the ADCOMS allows for substantial sample size reductions in non-enriched and enriched MCI populations even over a 12-month period by increasing sensitivity. This derived score has shown adequate sensitivity in the MCI due to AD amyloid confirmed (CSF Aβ-positive) subgroup.

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007).

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The CDR is a clinical global rating scale requiring the interviewing of both the subject and an informant who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The CBB is a brief, computer-administered cognitive test battery that requires approximately 10 minutes for administration (Darby, et al., 2012; Fredrickson, et al., 2008; Maruff, et al., 2009). The CBB has been used to detect cognitive impairment in several neurodegenerative conditions including the measurement of cognitive function in healthy older adults and in

adults with clinically diagnosed AD and prodromal AD (Darby, et al., 2009; Hammers, et al., 2012; Lim, et al., 2012a; Lim, et al., 2012b). The administration, scoring, and reporting of the CBB is automated and highly standardized, resulting in cognitive paradigms that have been well-validated in neuropsychological and cognitive studies (Fredrickson, et al., 2008; Maruff, et al., 2009). See Section 9.5.1.3.1 for further details.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al,. 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials on the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson et al., 2011, Lim, et al., 2012a, Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with E2609 treatment.

Volumetric magnetic resonance imaging is discussed in Section 9.2.5.4.

## 9.2.5 Rationale for Biomarkers

### 9.2.5.1 Overall Rationale

The biomarker strategy for this study includes the following aims:

- To establish an amyloid load in the brain at study entry (via the PET eligibility inclusion criterion)
- To evaluate safety (principally by MRI)
- To evaluate a PD effect in terms of both Aβ in CSF and brain amyloid assessed by amyloid PET and to establish that this PD effect is maintained long-term (revised per Amendment 02)
- To evaluate disease modification through longitudinal assessments of vMRI, amyloid PET, and CSF biomarkers of neurodegeneration (tau and p-tau)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

### 9.2.5.2 Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect of E2609 on Aβ(1-40) +Aβ(1-42) and other C-terminally truncated Aβ peptides such as Aβ(1-38) through inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using [$^{11}$C]PiB, suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain

parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases in CSF Aβ concentrations that are seen in AD are believed to be related to this decrease in brain Aβ availability.

Both total tau (t-tau) and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni and Bhaskar, 2012). CSF tau measurements have been correlated with cerebral atrophy, while their ratios with Aβ42 have provided useful predictors of cognitive decline and progression to dementia due to AD. Rebalancing dysregulated amyloid production early in the process may positively affect the neurodegenerative process and thus affect these markers and benefit the disease trajectory. Therefore, monitoring these markers in conjunction with amyloid imaging may provide further supportive evidence of efficacy.

Baseline levels of Aβ(1-42), tau, and p-tau will also help elucidate the extent of AD pathology at entry to the study and can be combined with baseline levels of *ApoE4* genotyping in addition to the baseline imaging variables to help explain differences in treatment response.

The study will be stratified at randomization for *ApoE4* gene status in order to account for any *ApoE* status by treatment interaction or *ApoE* status by amyloid-related imaging abnormalities risk interaction.

#### 9.2.5.3 Amyloid PET

Amyloid PET imaging will be used in this study for 2 primary reasons: 1) to confirm the presence of AD pathology in the brain of subjects with MCI/Prodromal AD or mild to moderate AD at entry to the study; and 2) to evaluate the effects of E2609 on amyloid levels in the brain, both by whole brain analysis (the average of 5 to 6 cortical regions) and brain region analysis. (revised per Amendment 01)

Longitudinal amyloid PET imaging will be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug) as an exploratory measure of the potential disease-modifying effects of E2609. Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses) and will only be conducted until 18-month PET scans of acceptable quality have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used. (Revised per Amendment 02)

#### 9.2.5.4 vMRI

Volumetric imaging will be used to evaluate the effects of E2609 on rates of atrophy across the different dose groups and to provide support that effective treatment is associated with modification of disease course (secondary endpoint for the MCI/Prodromal population and exploratory endpoint for the mild to moderate AD population). (revised per Amendment 01) A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal

regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. Clinically efficacious doses are predicted to be associated with a slowing in the rate of hippocampal atrophy compared with rates observed in the placebo and non-efficacious dose groups. Treatment effects on left and right hippocampal, whole brain, and total ventricular volumes are exploratory endpoints.

Annualized rates of change of 2% to 3% have been reported for the AD brain compared with 1% in MCI and <1% in age-matched controls (Hua, et al., 2010, Leung, et al., 2010). However, subjects with MCI due to AD-dementia (CSF Aβ <192 pg/ml or positive amyloid imaging) show rates of atrophy comparable to those observed in subjects with AD-dementia (Hua, et al., 2009; Hua, et al., 2010; Leung, et al., 2010; Morra, et al., 2009), supporting the notion that such subjects are on similar trajectories as those with mild AD-dementia. Lower levels of CSF Aβ42, amyloid positivity on PET imaging, and higher levels of CSF tau in addition to the presence of the *ApoE4* allele have all been associated with greater rates of brain atrophy (Fjell, et al., 2010a; Fjell, et al., 2010b) and will be entered as covariates in various analyses. Hippocampal atrophy has also been shown to predict clinical progression independently of amyloid levels in the brain (Jack, et al., 2010), and this measure will be entered as a covariate in the analysis of the clinical endpoints along with the aforementioned variables.

Brain volume (total ventricular volume, whole brain, temporal lobe) generally shows a modest correlation with performance on a number of cognitive scales (Hua, et al., 2009; Hua, et al., 2010; Freeborough, et al., 1997; Leung, et al., 2010). Using volumetric analysis performed at 6-month intervals, these relationships and the effects of E2609 treatment will be explored further. Recent advances in analysis software have made structural imaging more sensitive to detect small changes and able to reliably measure rates of atrophy at these intervals, particularly in the posterior parietal and the lateral temporal regions during the early stages of disease (Hua, et al., 2009; Hua, et al., 2010). Given these observations, a demonstration of significant slowing or stabilization in the rate of atrophy in response to treatment, compared with placebo, will offer further support for disease modification.

### 9.2.6 Clinical Risks and Mitigation Strategy

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, and to mitigate clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. These safety aspects include the following:

- Two-stage study design: there will be a pause in recruitment after 60 subjects have been randomized to study drug (Stage A). Only after the safety of E2609 in these first 60 subjects (consisting of up to 12 weeks data for the later subjects and longer dosing periods for the earlier subjects) has been reviewed by the DSMB and considered acceptable, will randomization of further subjects into the study commence (Stage B). (revised per Amendment 01)
- Immunology-related and infection-related exclusion criteria
- Review of unblinded safety data by an independent DSMB at regular intervals

- Safety criteria for discontinuation of study drug based on CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cell) and other lymphocytes (absolute counts and percentage change from baseline), skin rash, reoccurrence of herpes virus infections including any oral herpes, genital herpes or shingles, other infections, MRI changes, ECGs, and pregnancy.

In addition to the features above, other safety aspects of this study designed to mitigate clinical risk include the following:

- Blinded safety data will be monitored by Eisai at regular intervals during the course of the study
- Routine safety assessments will include the monitoring and recording of all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events. To assess potential immunomodulatory effects, peripheral blood mononuclear cells (PBMCs) will be collected at baseline, during treatment, and posttreatment.

As per the communication from the Food and Drug Administration (FDA) in Aug 2013, there are concerns that hypopigmentation of the skin and mucous membranes may occur with BACE1 inhibitory drugs. Although no such effects have been seen with E2609 to date, assessments by a reviewing dermatologist will be performed at regular intervals during the study. These assessments will be made centrally, using standardized photography and will specifically include evaluation of any areas of depigmentation or any rash. Dermatological assessments will be supplemented with a specific question to subjects regarding skin changes at each visit. Any such changes could be referred to the central reviewing dermatologist, and to a local dermatologist if needed, for further evaluation. See Section 9.5.1.5.8 for further details.

- Baseline and on-study blood and DNA samples will be taken and stored for all subjects, and CSF samples will be taken and stored for all subjects who consent to CSF sample collection (revised per Amendment 02). These samples may be tested in the event that a subject develops AEs that warrant further investigation (eg, if a subject develops a treatment-emergent infection) (see Section 9.5.1.2.2).
- Central reading of safety brain MRI assessments (including any MRI evidence of demyelination) will be performed at Screening, at approximately 6-month intervals during the Treatment Period, and at the final Follow-Up Visit.
- Full neurological examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations. Details of the neurological examination are given in Section 9.5.1.5.9.

- Cognitive decline will be assessed as a safety assessment (ADAS-cog$_{14}$, MMSE, and CBB). Of particular importance will be the assessment of reaction time testing using the detection and identification tasks on the CBB.
- An assessment of suicidality using the C-SSRS will be performed at Screening, Baseline, and at regular intervals during the Treatment and Follow-Up Period (see Section 9.5.1.5.11).
- All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will have at least 2 off-treatment Follow-Up visits (4 and 12 weeks after the last dose of study drug). More frequent safety assessments can be made as unscheduled assessments/visits during the off-treatment Follow-Up period, if clinically indicated.
- An ophthalmic examination will be conducted at Baseline and if the subject experiences visual disturbances during the course of the study (see Section 9.5.1.2.1).

## 9.3 Selection of Study Population

Stage A will randomize 60 eligible MCI/Prodromal or mild to moderate AD subjects at approximately 40 sites in the United States (revised per Amendment 02). There will be no restriction to the number of subjects from either population. Stage B will randomize subjects at approximately 125 sites globally. Recruitment will continue in Stage B until a maximum of approximately 500 MCI/Prodromal subjects and up to a maximum of approximately 200 mild to moderate AD subjects have been randomized (including subjects randomized during Stage A). The final total number of MCI/prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. The number of mild to moderate AD subjects randomized in Stage B will depend upon the number of mild to moderate AD subjects randomized during Stage A. (revised per Amendment 01)

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

### 9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD (Albert, et al., 2011) or AD dementia (McKhann, et al., 2011) and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at Screening Visit 1:**
(revised per Amendment 02)

a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation
b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT. Alternatively, cognitive impairment of at least 0.5 SD from age-adjusted

norms in delayed recall on the ISLT plus impairment of at least 1 SD from age-adjusted norms in at least 1 other computerized learning and memory test (ISLT immediate recall, or 1 of the learning and memory components of the CBB). (revised per Amendment 02)

c. FAQ ≤24 (revised per Amendment 01)

d. MMSE ≥16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading; an historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group (revised per Amendment 02)
3. Male or female, age 50 to 85 years, inclusive at time of consent
4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.
5. If receiving acetylcholinesterase inhibitor (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the Baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.
6. Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization

### 9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or MRI
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening

4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and <1cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could, in the opinion of the investigator, confound the MCI/Prodromal or mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendments 01 and 02)
7. A score of ≥8 on the 15-item Geriatric Depression Scale (GDS) at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the LLN for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
12. Any contraindications to LP for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity). Only applicable to subjects consenting to CSF sample collection (revised per Amendment 02)
13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of Ig deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis

16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization.
20. Any active infection within the last 4 weeks prior to randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below population-adjusted LLN at Screening or Baseline and confirmed by a repeat test conducted 1 week after the initial test. The population-adjusted LLN for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are 396, 157, and 74 cells/μL respectively. See Appendix 5. (revised per Amendment 02)
23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the Investigator and the Medical Monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of clinical immunodeficiency. The discussion with the Medical Monitor should include a detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)
24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate ECGs. A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute (bpm) at Screening or Baseline

29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.
33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo). Diagnosis of an underlying disease causing hypopigmentation is not necessary for exclusion if the clinical presentation is consistent with such a condition. Hypopigmentation associated with scarring need not be exclusionary. (revised per Amendment 02)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the C-SSRS suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation

42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period or for 28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.
    - Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.

      (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).
44. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or not practicing highly effective contraception throughout the study period or for 28 days after study drug discontinuation). No sperm donation is allowed during the study period and for 28 days after study drug discontinuation.

### 9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may discontinue study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to stop study drug or withdraw from the study at any time for any reason.

Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug (see Section 9.1.2.3). Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie, at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB and ISLT) will be conducted. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) after the Early Discontinuation Visit or within ± 8 days

of either of the Follow-Up Visits (Visit 19 and Visit 20). Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the Subject Disposition eCRF page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study drug and withdraws from the study at the same time, the ED Visit will be followed (see Section 9.5.5).

Safety-related criteria for discontinuation of study drug include the following:

a. A study drug discontinuation threshold will be set based on absolute counts of CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells). The discontinuation threshold will be set at below the level of the population-adjusted LLN (CD4=396 cells/µL; CD8=157 cells/µL; and CD19=74 cells/µL), at a level that represents a greater risk of opportunistic infection in the treated population. (revised per Amendment 02) For CD4 (T helper cells) the discontinuation threshold is 250 cells/µL. For CD8 (cytotoxic T cells) and CD19 (B cells) the discontinuation thresholds are 150 cells/µL and 50 cells/µL, respectively. Any subject who has CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below the discontinuation threshold as confirmed by a repeat test conducted within 1 week of the initial test will be discontinued from study drug.
b. Subjects with CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between the population-adjusted LLN and the discontinuation threshold will have lymphocyte subset counts performed on a weekly basis. (revised per Amendment 02) Subjects with a >33% reduction from baseline in CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts will also have lymphocyte subset counts performed on a weekly basis. During the early stages of the treatment period, where visits are conducted weekly (ie, Visits 4, 5, 6, and 7), lymphocyte subsets are already scheduled to be measured on a weekly basis and so additional visits or blood draws are not required. (revised per Amendment 02) For these subjects, the decision as to whether the subject remains on study drug or is to be discontinued from study drug will be based upon clinical judgment and will take into account any clinical presentation in addition to the lymphocyte subset counts. These subjects may continue with treatment if there is no clinical evidence of infection. They will be discontinued from study drug if they have infections of a moderate to severe intensity (eg, subjects whose infections are not localized, or are systemically unwell, or who require systemic anti-infective drug treatment).

**Table 1 Study Drug Actions for Lymphocyte Subset Absolute Counts**

| Lymphocyte subset absolute counts | Action | Decision to continue or discontinue |
|---|---|---|
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold | Retest within 1 week along with CBC with differentials | If retest performed within 1 week confirms lymphocyte subset counts below the discontinuation threshold, discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between population-adjusted LLN and discontinuation threshold or >33% reduction from baseline in CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts | Lymphocyte subset counts (and CBC with differentials) to be performed weekly until lymphocyte subset counts return to ≥ population-adjusted LLN or no more than 33% reduction from baseline | Decision will be based upon lymphocyte subset counts and clinical judgment |

LLN = lower limit of normal, CBC = complete blood count. (table revised per Amendment 02)

c. Subjects with clinical evidence of infection will have their CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts measured. Blood and other biological samples will also be collected for investigations of infective pathogens (eg, serological tests, quantitative polymerase chain reaction, microscopy, and culture) where appropriate. In subjects with infection, if any of their absolute cell counts meets the discontinuation thresholds, study drug will be discontinued. All subjects with severe infections will be discontinued from study drug. All subjects with herpes zoster (shingles) or ocular herpes infections will be discontinued from study drug, regardless of severity of presentation. Subjects with mild or moderate infection may continue treatment with study drug unless otherwise clinically indicated or otherwise specified below. Specifically, when any of the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are between the population-adjusted LLN and the discontinuation thresholds or have shown >33% reduction from baseline, subjects with infections of moderate intensity will be discontinued from study drug (eg, subjects whose infections are not localized, or subjects who are systemically unwell, or who require systemic anti-infective drug treatment). All subjects with infection who are discontinued from study drug will be followed for a period of 12 weeks or until the infection resolves/ stabilizes or until the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts have returned to greater than population-adjusted LLN (whichever comes latest). (revised per Amendment 02)

**Table 2 Study Drug Actions for Lymphocyte Subset Absolute Counts and Infection**

| Criterion | Severity of Infection | | | |
|---|---|---|---|---|
| | None | Mild | Moderate | Severe |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold | If confirmed with repeat testing within 1 week, then discontinue study drug. | Discontinue study drug | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between population-adjusted LLN and discontinuation threshold or >33% reduction from baseline in CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts always > population-adjusted LLN and no reduction from baseline >33% | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated (See (e) for exception) | Discontinue study drug |

LLN = lower limit of normal. Table revised per Amendment 02

d. A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (see (e) for exception), will be discontinued from study drug and a dermatological consult will be requested regardless of whether the rash is considered drug-related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatological consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

e. Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

f. Development of any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. If discontinued from study drug, subjects will undergo an ED Visit within 7 days after discontinuation and will attend the Follow-Up Visits 4 and 12 weeks after the last dose of study drug. They will also undertake an Unscheduled Visit (with MRI) at approximately 4 weeks after the visit at which such MRI features were first identified. An MRI will also be performed at approximately the time of the second Follow-Up Visit (Visit 20). Additional visits for safety may be arranged if clinically indicated in the opinion of the investigator, including after 12 weeks after the last dose of study drug. At any time during the treatment period, subjects who have asymptomatic, treatment-emergent microhemorrhages as detected by MRI, but none of the features which merit discontinuation of treatment (ie, vasogenic edema, macrohemorrhage, an area of

superficial siderosis, or a symptomatic treatment-emergent microhemorrhage) may continue with treatment. These subjects will have safety assessments (including MRI) at approximately 4 weeks after the visit at which such MRI features were found. They will also continue with the scheduled MRI scans. Additional unscheduled MRI scans may be arranged on an individual subject basis in discussion with the study medical monitor.

g. A postdose ECG with an average QTcF interval >500 msec from triplicate ECGs
h. A postdose ECG with a QTcF interval increase from baseline >60 msec and a QTcF interval >450 msec as demonstrated from triplicate ECGs
i. Any seizure (motor or non-motor)
j. Pregnancy

## 9.4 Treatments

### 9.4.1 Treatments Administered

For this study the test drug is E2609 and the control drug is placebo. All study drugs are to be administered orally, QD, with food.

Treatments to be administered in Stage A and Stage B are shown below and in Figure 1.

The 2 highest E2609 doses (15 and 50 mg) taken into Stage B, after the PK/PD and safety review from Stage A, will be used for the mild to moderate AD population in Stage B. (revised per Amendment 01)

- Stage A: 3 doses (5, 15, and 50 mg) of E2609 or placebo
- Stage B, MCI/Prodromal Cohort: 3 doses (5, 15, and 50 mg) of E2609 or placebo
- Stage B, Mild to Moderate AD Cohort: 2 doses (15 and 50 mg) of E2609 or placebo. (revised per Amendment 01)

Study treatment will begin on Day 1 (at the study site) following Randomization and will continue for approximately 78 weeks. Please refer to Table 7 and Section 9.5.1.4.1 for specific information on drug administration on days when PK sampling is to be performed.

Study drug doses will remain the same for each individual subject unless the interim PK/PD analysis determines that an entire dose level requires adjustment (Section 9.4.4). See Section 9.3.3 for safety-related discontinuation criteria of study drug. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

### 9.4.2 Identity of Investigational Product

E2609 tablets of 5-, 10-, and 25-mg dose strengths will be supplied. Placebo tablets of identical appearance will also be available. Each subject will receive 2 tablets, which combined will make up the required doses of E2609 5, 15, 50 mg, or placebo. The tablets

will be supplied by the Sponsor in labeled blister packs. The product release certificates for E2609 and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either E2609 or placebo, or both (see Section 9.4.2.3 for labeling details).

#### 9.4.2.1 Chemical Name and Formula of E2609

- Test drug code: E2609
- Generic name: not applicable
- Chemical name: International Union of Pure and Applied Chemistry
- *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

#### 9.4.2.2 Comparator Drug

Not applicable.

#### 9.4.2.3 Labeling for Study Drug

E2609 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier (ID)
- Lot number/batch number
- Storage conditions, expiration date if necessary

#### 9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data

acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

### 9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used for Stage A (all subjects), for Stage B MCI/Prodromal subjects and Stage B for mild to moderate AD subjects are described in Section 9.4.1. (revised per Amendment 01)

Randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized blister card identification numbers. At enrollment, the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 3), the IxRS will assign each subject a unique randomization number.

### 9.4.4 Selection of Doses in the Study

It is not known how the level of CSF or brain Aβ reduction is related to clinical efficacy. Therefore, in this study, doses will be selected such that at steady state, they will result in 25%, 50%, and 75% reduction in CSF Aβ levels from baseline to cover a broad range of PD effects.

In Study 007, the relative bioavailability of a tablet formulation of E2609 in the fed and the fasted states compared with the capsule formulation in the fasted state (used in Studies 001 and 002) was investigated. It was found that when the tablet form of E2609 (50 mg) was administered with food, the exposure (ie, AUC) of the parent drug E2609 was higher, with lower maximum observed concentrations and reduced exposure to the metabolites, compared with either formulation in the fasted state.

Based on the PK/PD modeling using data from healthy volunteer Studies 001, 002, and 007, doses of 5, 15, and 50 mg QD administered as the tablet formulation with food in this study should achieve CSF Aβ reduction from baseline of approximately 25%, 50%, and 75% at steady state, respectively (Table 3).

**Table 3 Predicted Steady State Plasma PK Parameters and CSF Amyloid β Reduction From Baseline**

| E2609 Tablet Daily Dose (mg) With Food | E2609 Plasma $C_{max,ss}$ (ng/ml) | E2609 Plasma $C_{ss,av}$ (ng/ml) | E2609 Plasma $AUC_{(0-24h)ss}$ (ng.h/ml) | % Reduction CSF BACE1 Activity | % Reduction CSF Aβ(1-x) |
|---|---|---|---|---|---|
| 5 | 6.2 | 3.3 | 80.3 | 16.2 | 33 |
| 15 | 18.6 | 10 | 240.9 | 36.6 | 56 |
| 50 | 62.1 | 33.5 | 803.0 | 65.7 | 79 |

Aβ(1-x) = amyloid beta monomer from amino acid 1 to x, $AUC_{(0-24h)ss}$ = area under the concentration x time curve at steady state from time zero to 24 hours, BACE1 = Beta-amyloid converting enzyme, CSF = cerebrospinal fluid, $C_{ss,av}$ = average steady-state concentration, $C_{max,ss}$ = maximum plasma concentration at steady state, PK = pharmacokinetics.

The PK/PD modeling described above, which was conducted using data obtained from healthy volunteers, has also been supported by modeling of data from subjects with an underlying AD pathology (Study 101). Furthermore, external data with another BACE1 inhibitor (MK-8931) showed a similar PD effect in AD patients as in healthy volunteers (Forman, et al., 2013). Therefore we are confident that the modeling of E2609 effects in healthy subjects will be applicable for both MCI/Prodromal and mild to moderate AD dementia patients. (revised per Amendment 01)

The exposure of the highest dose in this study (50 mg QD tablet administered with food) is less than that of the 100 mg QD dose (capsule administered fasted) in Study 002.

The 100 mg QD dose administered for 14 days in Study 002 was well tolerated with no clinically significant changes in laboratory parameters, vital signs, or ECG parameters. On Day 15, for the 100 mg QD cohort in Study 002, there was a reduction of CD4 lymphocyte counts compared with placebo (CD4 lymphocyte counts on E2609 decreased by 3.1% from baseline, whereas the placebo control showed an increase of 8.7%), but this decrease was less than that observed at doses of 200 mg (22.9% decrease) or 400 mg (17.3% decrease). No subjects had infections or drug rash while receiving E2609 100 mg QD or at lower doses in Study 002, whereas at 200 and 400 mg QD, 4 subjects had symptomatic orolabial HSV1 relapses and 2 subjects at the highest dose had drug rash. The highest dose for Study 202 of 50 mg QD (tablet administered with food) is therefore expected to have a similar or better safety profile compared with the 100 mg QD capsule (administered fasted) in Study 002. Specific exclusion criteria, blinded and unblinded safety monitoring procedures, and safety criteria for discontinuation from study drug are included in this study in order to mitigate any immunology-related risk with E2609, particularly in light of the progression from 14 days of dosing (Study 002) to 18 months of dosing in this study.

In Stage A, all subjects will be randomized to receive either placebo or E2609 at 5, 15, or 50 mg QD. In Stage B, subjects in the MCI/Prodromal cohort will continue to be randomized to receive either placebo or E2609 at 5, 15, or 50 mg QD. In Stage B, subjects in the Mild to Moderate AD cohort will be randomized to receive either placebo or E2609 at 15 or 50 mg QD, but not the 5-mg QD dose. The rationale for not including an E2609 5-mg QD dose in the dose regimens for Stage B subjects with mild to moderate AD is that more

advanced disease may require greater reduction in CSF Aβ levels for comparable effects. (revised per Amendment 01)

Interim analyses of the E2609 PK and PD profiles will be performed on subjects who have provided CSF samples at Baseline and after 4 weeks of study drug. These data will be used to evaluate the CSF PD effects of E2609 doses, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels. (revised per Amendments 01 and 02) The mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment for each dose of E2609 and its 90% confidence interval will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data from Stage A and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline after 4 weeks of dosing. (revised per Amendment 02)

If dose adjustment is required for Stage B, a protocol amendment reflecting the new doses will be submitted.

### 9.4.5 Selection and Timing of Dose for Each Subject

E2609 is administered orally, QD, with food. Study treatment will begin on Day 1 following randomization and will continue for approximately 78 weeks.

### 9.4.6 Blinding

E2609 and placebo will be administered as tablets of identical appearance.

During the Randomization Phase and Follow-Up Phases, subjects, caregivers/informants, and all clinical site personnel involved with the conduct and interpretation of the study, including investigators will be blinded to the treatment codes (double-blind). In order to make decisions about the remainder of the study as well as the full E2609 clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. (revised per Amendment 03)

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (ie, those who are trained and certified to perform the various cognitive assessments that are undertaken in this study). Furthermore, at the site, the notes and reports relating to safety assessments must be kept separate from the notes and reports relating to efficacy, particularly for the CDR. (revised per Amendment 01)

Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

The PK/PD interim analysis to evaluate the E2609 doses to be used for Stage B will be conducted by an independent group (revised per Amendment 02). Any changes to dose will be reflected in an amendment to the protocol and the Statistical Analysis Plan will detail how data will be handled in the primary analysis.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

At the conclusion of the study, all unused drug supplies are to be returned to the Eisai approved contract packaging vendor.

### 9.4.7 Prior and Concomitant Therapy

Medication (including over-the-counter medications) or therapy administered to the subject before the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2. Prohibited medications are presented in Listing 1, Listing 2, Listing 3, Listing 4, Listing 5, and Listing 6. Medications that are permitted with restrictions are listed in Listing 7, Listing 8, and Listing 9.

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit:

- Anticoagulants (eg, warfarin, digabatrin) are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization
- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization

Subjects taking AChEIs or memantine must meet the following criteria in order to be included in the primary analyses:

- On a stable dose for 12 weeks before the Baseline cognitive assessments at Visit 2
- Remain on a stable dose while on study

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for the primary analyses.

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety, and are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks.

### 9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period. CRAs will review treatment compliance during site visits and at the completion of the study.

### 9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted

- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the principal investigator including a copy of the principal investigator's current medical license (required for United States sites) or medical registration number on the curriculum vitae
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study

drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

## 9.5 Study Assessments

### 9.5.1 Assessments

#### 9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

#### 9.5.1.2 Baseline Assessments

Assessments to be made at Screening and Baseline and throughout the study are described in Section 9.5.1.3, Section 9.5.1.4, and Section 9.5.1.5.

##### 9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, current medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment due to AD. Subjects will be asked about history of TB, infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV Types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include onset, duration, relapse frequency, severity, and treatments. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The 15-item GDS and modified Hachinski ischemic scale will also be assessed at Screening as part of the exclusion criteria.

Physical examinations (complete or routine) will be performed as designated in Table 6. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, and skin, and a neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit

will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### 9.5.1.2.2 VIRAL TESTING

As specified in Table 6, blood will be collected for screening for Hepatitis B and Hepatitis C for determining eligibility, and at Baseline for viral characterization.

#### 9.5.1.2.3 B12 TESTING

Blood will also be collected for vitamin B12 levels as specified in Table 6.

#### 9.5.1.2.4 TB EXPOSURE TESTING

Blood will also be collected for testing for previous TB exposure, as specified in Table 6.

#### 9.5.1.2.5 URINE DRUG TESTING

Urine will be collected for drug screening as specified in Table 6.

### 9.5.1.3 Efficacy Assessments

#### 9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

The timing of psychometric assessments is shown in Table 6 and Table 7. These assessments should be administered in the morning (or, if not possible, consistently at the same time of day) and should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). At the Screening Visit, the recommended order of assessments is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. At the Baseline Visit, the assessments are to be conducted in the following order: MMSE, CDR, ADAS-cog$_{14}$, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). (revised per Amendment 02)

At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

**The Derived Alzheimer's Disease Composite Score:** The primary efficacy endpoint is the change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects.

The ADCOMS is derived from the ADAS-cog (4 items), the MMSE (2 items), and the CDR (all 6 items), described below. The ADCOMS is more sensitive to clinical progression compared with currently existing clinical batteries and requires smaller sample sizes for clinical studies in MCI/Prodromal AD or mild to moderate AD. (revised per Amendment 01)

It also shows sensitivity to treatment effects with AChEIs. The ADCOMS assesses both cognitive and functional domains and can be offered as a single primary clinical endpoint. The ADCOMS has a range from 0 to 1.97.

**CogState Brief Battery:** The CBB is a computer-based battery comprising 4 cognitive tests:

1. Detection – a simple reaction time test where the subject presses a key when the card is turned face up from a pack of cards ("Has the card turned over"). Speed of response is the measure.
2. Identification – a simple choice reaction time test where the subject presses 1 of 2 keys when the card just turned face up is either a red card or a black card ("Is the card red"). Speed of response is the measure.
3. One Card Back – a simple working memory test where the subject presses 1 of 2 keys when the card turned face up is either the card seen in the immediately previous trial or not ("Is the previous card the same"). Accuracy of response is the measure.
4. One Card Learning – a visual learning and memory test where the subject presses 1 of 2 keys depending on whether the card just turned face up has been seen before or not in the task ("Have you seen this card before in this task"). Accuracy of response is the measure.

**ISLT:** The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 15 minutes, in which time the CBB is performed, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

**Mini Mental State Examination:** A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

**Clinical Dementia Rating:** The CDR assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

**Alzheimer's Disease Assessment Scale - cognitive subscale:** Discussed in Section 9.2.4.

**Functional Assessment Questionnaire:** Either a caregiver or informant or the subject provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

#### 9.5.1.3.2 VOLUMETRIC MRI

Volumetric MRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the Alzheimer's Disease Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

Volumetric MRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. Volumetric MRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. Volumetric MRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 6 and Table 7, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

For subjects who consent to CSF sample collection, CSF samples will be collected by LP (gravity drip method) at the timepoints specified in Table 6 and Table 7 (revised per Amendment 02). The CSF sample taken at the Baseline Visit will only be performed after subjects consent to CSF sample collection, and after confirmation of an amyloid positive PET scan (revised per Amendment 02). See Section 9.5.1.4.2 for further details.

### 9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

#### 9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of E2609. For subjects who consent to CSF sample collection, CSF samples will be collected for the determination of E2609 concentrations. (revised per Amendment 02) Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with E2609.

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 6 and Table 7. Two PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visits 5, 11, 14, and 16, and 4 to 8 hours postdose at Visit 7 and Visit 18 (or at the ED Visit). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug with food at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or at the ED Visit) the PK blood sample should be collected shortly before or shortly after completing the LP. (revised per Amendment 01) Although the PK sampling procedures at the ED visit should follow those of Visit 18, in the event that study drug has already been discontinued prior to the ED visit, then no dosing will be conducted. However, a PK sample at trough (before LP) will be collected, followed by LP at approximately the same time as previous visits. A second PK blood sample will be collected as close as possible in time to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

#### 9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

**Biomarkers**

Subjects who consent to CSF sample collection will be encouraged to stay at the site after completion of LP for medical observation (revised per Amendment 02). At Baseline, a CSF sample will be collected by LP (gravity drip method) after fasting (preferred), or at least 2 hours after the most recent meal. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. At visits where cognitive tests are also performed, if the tests are to be performed on the same day, the LP must be performed after the cognitive tests have been completed and the subjects should rest and drink some fluid to hydrate before the LP. (revised per Amendment 01) The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. The CSF sample will be used for PD assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), t-tau, p-tau, and BACE. The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses (eg, miRNA). Aβ(1-x) in both CSF and plasma will be measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and post-screening analysis of CSF Aβ(1-42), t-tau, and p tau will be performed using ELISAs. BACE1 levels will be measured using internally developed fluorescence resonance energy transfer and ELISA based assay(s). Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

The blood sample collected for PD analyses at Baseline should be collected on the same day shortly before or shortly after completing the LP at Baseline. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

At the Baseline Visit, blood samples will be collected and stored for determination of prior exposure to any suspected infective agents in the event that the subject develops treatment-emergent AEs that warrant further investigation (eg, treatment-emergent infection). For subjects who consent to CSF sample collection, CSF samples from the Baseline Visit will also be stored for the same purpose. (revised per Amendment 02) Testing may include, but not be limited to, serological tests, viral titer by quantitative polymerase chain reaction, or human leukocyte antigen genotyping.

Blood samples will be collected for PD assessments as specified in Table 6 and Table 7. See Section 9.5.1.4.2 for further details.

For all subjects, baseline and on-study blood samples, DNA samples, and any CSF samples collected from subjects who consent to CSF collection will be stored for up to 15 years. (revised per Amendment 02)

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

**Pharmacogenomics**

A blood sample will be obtained at Baseline and will be used to determine the *ApoE* genotype (homozygous or heterozygous E4 versus non-E4) and the *NAT2* phenotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response, safety, or PK of E2609. Details of which genotype / phenotype data will be applied to the analyses of efficacy, safety or PK will be discussed in the Statistical Analysis Plan.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

**Amyloid PET**

An amyloid PET scan will be performed at Screening to confirm deposition of amyloid in the brain. An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02) Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on

subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses) and will only be conducted until acceptable 18-month PET scans have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used (Table 6). (revised per Amendment 02) PET scanning will be performed with a locally approved Aβ imaging agent (eg, Amyvid). Descriptions and detailed instructions for all imaging can be found in the imaging manual.

Amyloid PET imaging is an exploratory measure of the potential disease-modifying effects of E2609.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, lymphocyte subsets, Igs, and urine values; periodic measurement of vital signs and ECGs; performance of physical and neurological examinations; centralized dermatological assessments; the C-SSRS; and safety MRIs as detailed in Table 6 and Table 7 will also be conducted. Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and posttreatment for exploratory immunomodulatory and immune-based analyses.

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (see Section 9.4.6). (revised per Amendment 01)

##### 9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E2609.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: It is not necessary to report every sign or symptom as a separate AE if the overall disease [diagnosis] is being reported as an AE.)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)

- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, discontinuation of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 20, as shown in Table 7). For subjects who discontinue early from study drug but undertake further efficacy assessments, AEs will only be collected for 3 months after the last dose of study drug, ie, through to the second follow-up visit (Visit 20). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF. SAEs will be collected for 3 months after the last dose of study drug, ie, through to the second follow-up visit (Visit 20). For subjects who discontinue early from study drug but continue with further efficacy assessments, SAEs will be solicited only for 3 months after the last dose of study drug, i.e. up to the 2nd follow up visit (Visit 20). However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the ADCOMS, ADAS-cog$_{14}$, MMSE, and CBB (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 4.

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal

- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis
- Dissociative state

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.11 for a description of the C-SSRS).

The following adverse events will require the collection of information sufficient to provide a detailed description of the event, treatment and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection; any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a "yes" answer to Type 4 or 5 suicidal ideation, or a "yes" response to any suicidal behavior on the C-SSRS.

All AEs must be followed through the second follow-up visit (Visit 20), or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

**Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.**

### Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

| | |
|---|---|
| Mild | Discomfort noticed, but no disruption of normal daily activity |
| Moderate | Discomfort sufficient to reduce or affect normal daily activity |
| Severe | Incapacitating, with inability to work or to perform normal daily activity |

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

## Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

*Classification of Causality*

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

#### 9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reportable using the criteria of important medical event if the event does not meet other serious criteria: new onset seizures, ocular herpes.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the eCRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

#### 9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 4. Subjects should be in a seated or supine position during blood collection. Table 6 and Table 7 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

See Section 9.3.3 for safety criteria for discontinuation from study drug related to absolute counts of CD4, CD8, and B lymphocytes, and for lymphocyte subset counts.

**Table 4 Clinical Laboratory Tests**

| Category | Parameters |
|---|---|
| **Hematology** | Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils).<br><br>PT, PTT, and INR (Screening and Baseline only) (revised per Amendment 02) |
| **Chemistry** | |
| **Electrolytes** | Bicarbonate, calcium, chloride, phosphate, potassium, sodium |
| **Liver function tests** | Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin |

## Table 4 Clinical Laboratory Tests

| Category | Parameters |
|---|---|
| **Renal function tests** | Blood urea/blood urea nitrogen, creatinine |
| **Other** | Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid |
| **Urinalysis** | Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells |
| **Other** | Lymphocyte subset analyses (see Table 5). Regulatory T cells will be measured using CD4, CD25, and FoxP3 intracellular marker.<br>PBMCs (revised per Amendment 02)<br>Ig analyses (IgG, IgA, and IgM).<br>Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]).<br>Viral characterization (including HSV1, HSV2 and CMV, etc)<br>Serum pregnancy test (females of child bearing potential only)<br>Tuberculosis Interferon Gamma Release Assays<br>Tests for thyroid function (thyroid stimulating hormone, free triidothyronine and free thyroxine) and vitamin B12<br>Blood sample for storage for subsequent testing of immune status<br>Cerebrospinal fluid sampling |

Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials, must also be repeated. (revised per Amendment 02)

CMV = cytomegalovirus, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV = herpes simplex virus, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PT = prothrombin time, PTT = partial thromboplastin time.

The 8 different surface markers (CD3, CD4, CD8, CD45, CD19, CD16, CD56, and CD14) and total lymphocyte counts will be measured in order to provide the lymphocyte subset data as shown in Table 5. In addition, Regulatory T cells will be measured using CD4, CD25, and FoxP3 intracellular marker. Current sponsor data supports the literature showing there is an age-related decline in lymphocyte subsets (see Appendix 5). These data have been used to revise the LLNs for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts to the population-adjusted LLNs of 396, 157, and 74 cells/µL, respectively) (revised per Amendment 02).

**Table 5 Lymphocyte Subtyping**

| Cell Type | Cell Surface Markers |
|---|---|
| T lymphocytes | CD3 |
| T helper cells | CD3+, CD4 |
| Cytotoxic T cells | CD3+, CD8 |
| Mature B cells | CD3-, CD19 |
| Natural killer cells | CD3-, CD16, CD56 |
| Macrophages | CD14 |

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the case report form [CRF] Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

#### 9.5.1.5.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [bpm], respiratory rate [per minute], body temperature [in centigrade], and weight [kg]) will be obtained at the visits designated in Table 6 and Table 7 by a validated method. Measurements of sitting BP and heart rate will be obtained. All BP measurements should be performed on the same arm, preferably by the same person.

#### 9.5.1.5.5 Physical Examinations

A complete physical examination will be performed at Screening as described in Section 9.5.1.2.1. At Baseline and during the Randomization Phase, routine physical examinations will take place as shown in Table 7. These examinations will include the cardiovascular system, respiratory system, and neurological system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.6 Electrocardiograms

Electrocardiograms will be obtained as designated in Table 6 and Table 7. Twelve-lead standard ECGs will be recorded in triplicate (1 minute apart) after subjects have been resting in the supine position for at least 5 minutes.

On any study day when ECG, vital signs, and blood samples are taken, these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.7 SAFETY MRI

Safety brain MRI assessments will be performed at the times shown in Table 6 and Table 7. Additional safety MRI scans can be performed at unscheduled visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Safety MRIs will be acquired using a standardized procedure that will include fluid-attenuated inversion recovery (FLAIR), gradient-echo, T1, and diffusion-weighted sequences to determine the presence of focal lesions including, but not limited to, evidence for ischemic and hemorrhagic stroke, subdural hematoma, neoplasm, arteriovenous malformation, micro and macrohemorrhages, superficial siderosis, lacunar infarcts, white matter abnormalities, and vasogenic edema. The imaging sequence for the Screening/safety MRI will include: T2 weighted anatomic MRI to rule out major white matter changes, cerebral infarction or other structural lesions, and a high-resolution 3D T1-weighted scan with isotropic voxels with volumes of 1 $mm^3$ or less. In addition, both FLAIR for the detection of vasogenic edema and T2* Gradient Recall Echo for the detection of microhemorrhages will be acquired. The 3D dataset will be reconstructed in transverse slices in Digital Imaging and Communications in Medicine format. The results of this MRI assessment will also be used as the Baseline Period MRI, against which changes after drug administration will be compared. Further details of the MRI protocol can be found in the Imaging Acquisition Guideline. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, and 18 and at the second Follow-Up Visit (Visit 20). In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

At any time during the treatment period, subjects will be discontinued from study drug if they develop any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. All of these features must be reported as study specific AEs (or AEs of special interest). These subjects will undergo an ED Visit within 7 days after discontinuation and Follow-Up Visits at 4 weeks and 12 weeks after the last dose of treatment. Subjects will also undertake an Unscheduled Visit (with MRI) at approximately 30 days after the visit at which such MRI features were first

identified. Additional visits may be arranged if clinically indicated in the opinion of the investigator, and may occur later than 12 weeks after the final dose of study drug.

#### 9.5.1.5.8 DERMATOLOGICAL ASSESSMENT

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at the times shown in Table 6 and Table 7. These assessments will specifically include evaluation of any areas of depigmentation or any rash.

In addition, subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregiver or informants will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or infection, and the investigator will be required to review such AEs as soon as possible and consider an unscheduled physical and dermatological evaluation. Detailed characteristics of any skin rashes will be captured in the clinical database. Physical examination may be undertaken where indicated. Treatment-emergent abnormal dermatological findings should be reported as AEs.

#### 9.5.1.5.9 NEUROLOGICAL EXAMINATION

Neurological examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations as shown in Table 6 and Table 7. Details of these examinations will be captured in an eCRF. The neurological examinations will monitor for new symptoms and signs which will then alert the investigator to consider new CNS pathology (especially slowly-evolving neurological conditions that may not lead to prominent symptoms). Examples of neurological signs that may indicate new CNS pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. In such a situation, the investigator should consider (but not limited to) demyelination in the differential diagnoses, and should discuss with the sponsor's medical monitor further investigations or treatment, which will be decided case by case. Neurological examinations will also include the assessment of cranial nerve function, especially the olfactory nerve. Treatment-emergent abnormal neurological findings should be reported as AEs.

#### 9.5.1.5.10 PREGNANCY TEST

At Screening, females of childbearing potential will have a serum pregnancy test. At Baseline and during the Treatment Period, urine samples will be obtained from females of childbearing potential for pregnancy tests (see Table 7).

#### 9.5.1.5.11 COLUMBIA SUICIDE SEVERITY RATING SCALE

An assessment of suicidal ideation and behavior using the C-SSRS will be performed at the designed time points in Table 6 and Table 7. A "yes" answer to Type 4 or 5 suicidal ideation or a "yes" response to any suicidal behavior queries will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

#### 9.5.1.5.12 BIOMARKER SAMPLES

As noted in Section 9.5.1.4.2, CSF (for subjects who consent to CSF sample collection), blood, and DNA samples will be collected and may be used for exploratory biomarker analyses, as well as tested in the event that a subject develops AEs that warrant further investigation. (revised per Amendment 02)

#### 9.5.1.5.13 OPHTHALMIC EXAMINATIONS

An ophthalmic examination will be conducted at Baseline (unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available). An additional examination will be conducted, if the subject experiences visual disturbances during the course of the study or is medically indicated. The ophthalmic examinations should include fundoscopy to look at the optic disc, macula and the rest of the retina, as well as an assessment of visual acuity and visual fields.

### 9.5.2 Schedule of Procedures/Assessments

#### 9.5.2.1 Schedule of Procedures/Assessments

Table 6 presents the Schedule of Procedures/Assessments for the Prerandomization Phase. Screening assessments will be organized into 4 tiers (see below and Figure 2).

Table 7 presents the Schedule of Procedures/Assessments for the Randomization Phase.

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

| Phase | Prerandomization | |
|---|---|---|
| Period | Screening | Baseline |
| Visit | 1 | 2 |
| **Procedures/ Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)** | | |
| Informed consent (subject and caregiver or informant) | X (Tier 1) | |
| Subject informed consent for CSF sample collection (voluntary) | X | X |
| Demographics | X (Tier 1) | |
| Medical history[a] | X (Tier 1) | |
| Prior / concomitant medications[b] | X (Tier 1) | X |
| Vital signs including weight[c] | X (Tier 1) | X |
| Height | X (Tier 1) | |
| Complete physical examination | X (Tier 1) | |
| Routine physical examination | | X |
| CBB and ISLT[d] | X (Tier 1) | X |
| MMSE[d] | X (Tier 1) | X |
| CDR[d] | X (Tier 1) | X |
| FAQ[d] | X (Tier 1) | X |
| ADAS-cog14[d] | | X |
| 15-item Geriatric Depression Scale | X (Tier 2) | |
| Modified Hachinski ischemic scale | X (Tier 2) | |
| C-SSRS | X (Tier 2) | X |
| 12-lead ECG[e] | X (Tier 2) | X |
| Blood and urine for clinical laboratory tests[f] | X (Tier 2) | X |
| Blood for lymphocyte subset analyses[g] | X (Tier 2) | X |
| Blood for Ig analyses[h] | X (Tier 2) | X |
| Blood for viral screen[i] | X (Tier 2) | |
| Blood for thyroid function tests[j] | X (Tier 2) | |
| Blood for vitamin B12 test | X (Tier 2) | |
| Test for previous TB exposure | X (Tier 2) | |
| Urine drug screen | X (Tier 2) | |
| Serum pregnancy test (females of childbearing potential only) | X (Tier 2) | |
| Urine pregnancy test (females of childbearing potential only) | | X |
| Safety and Volumetric MRI[k] | X (Tier 3) | |
| Amyloid PET scan[l] | X (Tier 4) | |
| Inclusion and Exclusion criteria | X (All tiers) | X |
| Adverse events | X (All tiers) | X |
| CSF sampling for PK, PD and storage[m] | | X |
| Blood sample for PK assessments[n] | | X |
| Blood sample for PD and exploratory biomarker assessments[o] | | X |
| Blood sample for pharmacogenomics | | X |
| Blood sample for storage for immune status[p] | | X |
| Blood sample for PBMC isolation | | X |
| Blood sample for viral characterization[q] | | X |
| Centralized dermatological assessment via photography[r] | | X |
| Neurological examinations[s] | | X |
| Ophthalmic assessment[t] | | X |

Table revised per Amendment 02

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

AChEI = acetylcholinesterase inhibitor, AD = Alzheimer's disease, ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CDR = Clinical Dementia Rating, CMV = cytomegalovirus, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), Ig = immunoglobulin, INR = International Normalized Ratio, ISLT = International Shopping List Task (immediate and delayed recall), LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetics, PET = positron emission tomography, PT = prothrombin time, PTT = partial thromboplastin time, TB = tuberculosis.

Note: Screening assessments/procedures have been organized into 4 distinct tiers. All assessments and procedures in each tier should be completed (see Figure 2), and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures, as long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. Similarly, all screening assessments and procedures must be completed, and eligibility to continue in the study confirmed, before any baseline assessments and procedures commence. Adverse events and eligibility against inclusion and exclusion criteria must be assessed at each stage within the Screening Visit and at the Baseline Visit. (revised per Amendment 01)

Note: All screening and baseline assessments are to be completed within 50 days, plus an additional window of up to 30 days if required (revised per Amendment 02). The interval between availability of the results of the last screening assessment (PET scan) and the first baseline (Visit 2) assessments should be as short as possible and ideally should not exceed 7 days. Visit 3 (Randomization) (see Table 7) should occur no more than 10 days after completion of the Baseline visit (Visit 2) and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion No.20 into account (revised per Amendment 02). Thus, the total Prerandomization Phase may be up to 60 days, plus an additional window of up to 30 days if required (revised per Amendment 02).

a: To include: mild cognitive impairment and AD history; history of TB, vaccination history against and infections due to varicella zoster virus (chickenpox and herpes zoster or shingles); infections due to HSV1 (orolabial herpes or cold sores) and 2 (genital herpes). Medical history of infections to include: onset, duration, relapse frequency, severity, and treatments. For any active infection within the last 4 weeks prior to randomization, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)

b: Prior and concomitant medications include AChEIs and memantine, and other medications for cognitive decline.

c: Weight, respiratory rate, body temperature, and sitting blood pressure and heart rate will be obtained.

d: To be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). At the Screening Visit, the recommended order of assessments is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. At the Baseline Visit, the assessments are to be conducted in the following order: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). (revised per Amendment 02) At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

e: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

f: Clinical laboratory tests consist of hematology (including PT, PTT, and INR), clinical chemistry, and urinalysis.

g: Lymphocyte subsets to be measured include CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cells), CD16/CD56 (natural killer cells) and CD14 (macrophages). Regulatory T cells will also be measured (CD4, CD25, FoxP3). Viability staining may also be employed. Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials, must also be repeated. (revised per Amendment 02)

h: Igs to be analyzed include IgG, IgA and IgM.

i: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

j: Thyroid function tests include thyroid stimulating hormone, free triidothyronine and free thyroxine.

k: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images. MRI will be read by an approved central reader. Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

assessments in the same imaging session. (revised per Amendment 01)

l: PET scanning will be performed with a locally approved β-amyloid imaging agent, eg, Amyvid if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. The PET image will be centrally read for the purpose of determining eligibility for inclusion into the study. An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02)

m: For subjects who consent to CSF sample collection: CSF will be collected by LP after fasting (preferred), or at least 2 hours after the most recent meal. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 and Visit 18) can be performed at a similar time of day (±1 hour) for each individual subject. If the LP and cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. The CSF sample will be used for PK and PD assessments. A CSF sample will also be stored for testing in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection). (revised per Amendments 01 and 02)

n: The PK blood sample should be collected on the same day shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

o: The PD and exploratory biomarker blood sample should be collected shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

p: A blood sample will be collected at Baseline and stored. This sample may be used for exploratory biomarkers associated with study drug or disease, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

q: Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

r: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. See Section 9.5.1.5.8 for further details.

s: To be performed by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations. Section 9.5.1.5.9 details what is included in the neurological examination.

t: An ophthalmic examination will be conducted at Visit 2 unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available. The ophthalmic examination should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields.

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| Phase | Randomization | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Period | Treatment | | | | | | | | | | | | | | | | | Follow-Up | | |
| Visit[a] | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | ED[b] | 19[c] | 20[c] | UNS Visit[d] |
| Day | 1 | 8 | 15 | 22 | 29 | 43 | 57 | 71 | 85 | 113 | 141 | 183 | 274 | 365 | 456 | 547 | | 575 | 631 | |
| Week | 1 | 2 | 3 | 4 | 5 | 7 | 9 | 11 | 13 | 17 | 21 | 27 | 40 | 53 | 66 | 79 | | 83 | 91 | |
| Weeks elapsed since first dose | 0 | 1 | 2 | 3 | 4 | 6 | 8 | 10 | 12 | 16 | 20 | 26 | 39 | 52 | 65 | 78 | | 82 | 90 | |
| Nominal months elapsed since first dose | 0 | | | | 1 | | 2 | | 3 | 4 | 5 | 6 | 9 | 12 | 15 | 18 | | 19 | 21 | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | |
| Routine physical examination | X | | | | X | | X | | X | | | X | X | X | X | X | X | X | X[e] | X |
| Inclusion and Exclusion criteria | X | | | | | | | | | | | | | | | | | | | |
| Vital signs[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[e] | X |
| Respiratory rate | | | | | X | | X | | X | X | X | X | X | X | X | X | X | X | X[e] | X |
| Weight | | | | | | | | | X | | | X | X | X | X | X | X | | X | X |
| Centralized dermatological assessment via photography[g] | | | | | | | | | X | | | X | X | X | X | X | X | | X | X |
| Neurological examination[h] | | | | | | | | | | | | X | | X | | X | X | X | X | X |
| Ophthalmic examination[i] | | | | | | | | | | | | | | | | | | | | X |
| Concomitant medications[j] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG[k] | | | X | | X | | X | | X | | | X | | X | | X | X | X | X[e] | X |
| Clinical biochemistry and urinalysis | | | X | | X | | X | | X | | | X | X | X | X | X | X | X | X | X |
| Complete blood count | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood samples for lymphocyte subset analyses[l] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood samples for Igs[m] | | | | | X | | X | | X | | | X | | X | | X | X | X | X | X |
| Blood samples for isolation of PBMCs | | | X | | | | | | X | | | | | | | | | | X | |
| Urine pregnancy test (females of CBP only) | X[n] | | | | | | | | X | | | X | X | X | X | X | X | X | | X |
| Blood sample for storage for immune status[o] | | | | | X | | | | X | | | X | | X | | X | X | X | X | X |
| CBB and ISLT[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| MMSE[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| CDR[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| ADAS-cog$_{14}$[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |

**Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)**

| **Phase** | **Randomization** | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | | | | | **Follow-Up** | | |
| **Visit**[a] | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **ED**[b] | **19**[c] | **20**[c] | |
| **Day** | **1** | **8** | **15** | **22** | **29** | **43** | **57** | **71** | **85** | **113** | **141** | **183** | **274** | **365** | **456** | **547** | | **575** | **631** | **UNS Visit**[d] |
| **Week** | **1** | **2** | **3** | **4** | **5** | **7** | **9** | **11** | **13** | **17** | **21** | **27** | **40** | **53** | **66** | **79** | | **83** | **91** | |
| **Weeks elapsed since first dose** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **10** | **12** | **16** | **20** | **26** | **39** | **52** | **65** | **78** | | **82** | **90** | |
| **Nominal months elapsed since first dose** | **0** | | | | **1** | | **2** | | **3** | **4** | **5** | **6** | **9** | **12** | **15** | **18** | | **19** | **21** | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | |
| FAQ[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| C-SSRS | | | | | X | | X | | X | | | X | X | X | X | X | X | X | X[e] | X |
| Safety and Volumetric MRI[q] | | | | | | | | | | | | X | | X | | X | X | | X | X |
| Amyloid PET[r] | | | | | | | | | | | | | | | | X | X | | | |
| Telephone contact[s] | | | X | | X | | | | X | | | X | | X | | X | X | | | X |
| Blood samples for PK[t] | | | X | | X | | | | X | | | X | | X | | X | X | | | X |
| Blood samples for PD and exploratory biomarkers[u] | | | X | | X | | | | X | | | X | | X | | X | X | X | X | |
| CSF sampling for PK and PD[v] | | | | | X | | | | | | | | | | | X | X | | | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Sleep/dream questionnaire[w] | | | | | | | | | | | | | | | | | | | | X |
| Randomization | X | | | | | | | | | | | | | | | | | | | |
| Dispense study drug[x] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |

**Notes for Table 7**

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating scale, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), Ig = immunoglobulin, ISLT = International Shopping List Task, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, UNS = unscheduled.

a: Visit 3 should be conducted no more than 10 days after completion of the Baseline visit (Visit 2) assessments and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion #20 into account. (revised per Amendment 02) A window of ±3 days will be permitted for Visit 4 to 14 inclusive. A window of ±10 days will be permitted for Visit 15 to 18 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since first dose" at subsequent visits.

b: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 19 and Visit 20, respectively). Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie. at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB, and ISLT) will be conducted. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) after the Early Discontinuation Visit or within ± 8 days of either of the Follow-Up Visits (Visit 19 and Visit 20). Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

c: All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 19 and Visit 20 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up period.

d: Unscheduled visits may be conducted at any time that safety or safety MRI data indicate per protocol or as clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

e: Only if clinically significant abnormalities are found at Visit 19 and the investigator considers it necessary to repeat at Visit 20. Clinical biochemistry, urinalysis, CBC, lymphocyte subsets and Igs should always be performed at Visit 20, regardless of clinical significance at Visit 19. (revised per Amendment 02)

f: Measurements of body temperature and sitting blood pressure and heart rate will be obtained.

g: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. Additional UNS dermatological assessments should be conducted in response to any dermatological AEs of concern (eg, depigmentation, rash, herpetic lesion).

h: Examples of neurological signs that may indicate new central nervous system pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

i: If the subject experiences visual disturbances during the course of the study, the subject will be referred to a specialist for a further ophthalmic examination, which should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields

j: Please refer to Section 9.4.7, which details prohibited and permitted medications in the study and associated timeframes.

k: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

l: Lymphocyte subsets to be measured include CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [NK cells] and CD14 [macrophages]) and total

lymphocytes. Regulatory T cells will also be measured (CD4, CD25, and FoxP3). Viability staining may also be employed. Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a Complete Blood Count, with differentials, must also be performed. (revised per Amendment 02)

m: Igs to be analyzed include IgG, IgA, and IgM.

n: An additional assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

o: Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

p: These assessments are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The order of assessments will be: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). At visits where the CDR or FAQ are conducted, the investigator will determine whether the informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

q: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images in MRI will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, and 18 and 20. In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A volumetric MRI sequence will be collected in all subjects immediately following all safety MRI assessments. (revised per Amendment 01)

r: PET scanning will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks. A PET scan will only be performed at Visit 18 or ED if the subject has a valid Screening PET scan for the purposes of longitudinal analyses; subjects who were determined to be eligible for the study on the basis of an historical PET scan will not have a PET scan performed at Visit 18 or ED (revised per Amendment 02)

s: Site staff will contact the subject or the caregiver or informant the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the caregiver or informant, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

t: Two plasma PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visit 5, Visit 11, Visit 14 and Visit 16 and 4 to 8 hours postdose at Visit 7 and Visit 18 (or ED). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or ED) the PK blood sample should be collected shortly before or shortly after completing the LP. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected, followed by LP at approximately the same time as at previous visits. A second PK blood sample will be collected as close as possible to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

u: PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day. At Visits 5, 11, 14, and 16 the PD blood samples should be collected predose.

v: For subjects who consent to CSF sample collection: All visits at which CSF samples are scheduled to be taken also include blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Baseline LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If the LP and the cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the

CSF sample will still be collected unless it was already collected within the past 3 months. (revised per Amendments 01and 02)

w: Subjects reporting adverse events relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

x: The first dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time as determined by the PI or Safety Physician for postdose medical observation. (revised per Amendment 02)

#### 9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 6 and Table 7 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 4 tiers (see Table 6, Section 9.1.1.1, and Figure 2.

See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 8 presents the number of blood and CSF samples, and the total volume of blood and CSF that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety.

**Table 8 Summary of Blood and CSF Sample Volumes**

| Assessment | Total number of collection time points | Number of time points x volume per collection (mL whole blood or CSF) | | Total volume (mL whole blood or CSF) |
|---|---|---|---|---|
| | | Screening and Baseline Periods | Treatment and Follow-Up Periods | |
| **Blood** | | | | |
| Chemistry | 12 | 2 x 2 mL | 10 x 2 mL | 24 mL |
| Hematology | 18 | 2 x 5 mL | 16 x 5 mL | 90 mL |
| Lymphocyte subset analyses | 18 | 2 x 4 mL | 16 x 4 mL | 72 mL |
| PBMC | 4 | 1 x 16 mL | 3 x 16 mL | 64 mL |
| IgA, IgM, IgG | 9 | 2 x 2 mL | 7 x 2 mL | 18 mL |
| PT, PTT for INR | 2 | 2 x 3 mL | None | 6 mL |
| Thyroid function tests (thyroid stimulating hormone, free triidothyronine and free thyroxine) | 1 | 1 x 3 mL | None | 3 mL |
| Viral screen (Hepatitis B and C) | 1 | 1 x 4 mL | None | 4 mL |
| Viral characterization | 1 | 1 x 4 mL | None | 4 mL |
| Vitamin B12 | 1 | 1 x 2 mL | None | 2 mL |
| Serum pregnancy test | 1 | 1 x 2 mL | None | 2 mL |
| Tuberculosis (interferon-gamma release assays) | 1 | 1 x 3 mL | None | 3 mL |
| Sample for immune status | 8 | 1 x 4 mL | 7 x 4 mL | 32 mL |
| PD sample | 9 | 1 x 4 mL | 8 x 4 mL | 36 mL |
| PK analysis | 7 | 1 x 3 mL | 6 x 6 mL | 39 mL |
| Pharmacogenetic sample | 1 | 1 x 3 mL | None | 3 mL |
| All blood samples, total volume whole blood collected | | 80 mL | 322 mL | 402 mL |
| **CSF (For subjects who consent to CSF sample collection) (revised per Amendment 02)** | | | | |
| PD and PK samples | 3 | 1 x 12 mL | 2 x 12 mL | 36 mL |

CSF = cerebrospinal fluid, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetic, PT = prothrombin time, PTT = partial thromboplastin time.

### 9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include vital signs, clinical laboratory assessments, physical examinations, ECG measurements, and reports of AEs. MRI will be used to detect vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage and is a standard evaluation to ensure subject safety. The C-SSRS has been endorsed by the FDA as a measure of potential suicidality (Guidance for Industry Suicidality).

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, in addition to mitigating clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. Details are provided in Section 9.2.6.

### 9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

#### 9.5.4.1 Reporting of Serious Adverse Events

**All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.**

SAEs, regardless of causality assessment, must be collected up to 3 months after the last dose of study drug, ie, through to the second follow-up visit (Visit 20). In subjects who discontinue study drug early, but continue with efficacy assessments, SAEs only need to be solicited up to 3 months after the last dose of study drug. However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

**For urgent safety issues**, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

#### 9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must discontinue study treatment.

#### 9.5.4.3 Reporting of Events Associated with Special Situations

##### 9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

| | |
|---|---|
| Overdose | Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose |
| Misuse | Intentional and inappropriate use of study drug not in accordance with the protocol |
| Abuse | Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects |
| Medication error | Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject |

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

#### 9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2) should always be considered serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

### 9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

### 9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

#### 9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

### 9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue study drug or withdraw from the study at any time for any reason. All subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 19 and Visit 20, respectively) (see Section 9.1.2.3). See Table 7 for full details of the assessments to be performed at these visits. Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie, at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog14, FAQ, CBB and ISLT) will be conducted. Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above. Subjects who discontinue study drug early (as opposed to subjects whose dosing with study drug is temporarily suspended under Medical Monitor guidance) will not be permitted to restart study drug.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and will provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who withdraw prematurely from the study will be withdrawn for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for withdrawal from the study. Study disposition information will be collected on the Subject Disposition eCRF.

A subject removed from the study for any reason may not be replaced.

### 9.5.6 Abuse or Diversion of Study Drug

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Potential Abuse-related Medication Handling Event eCRF.

### 9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

## 9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

### 9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

### 9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy assessments performed in this study.

## 9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, except for the Bayesian methods on the primary endpoint.

### 9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the statistical analysis plan, which will be finalized before the first interim efficacy analysis.

#### 9.7.1.1 Study Endpoints

See Section 9.2.3 for a discussion of the rationale for the selection and clinical relevance of the primary study endpoint. Further information on the derived ADCOMS is described in Section 9.5.1.3.1.

##### 9.7.1.1.1 PRIMARY ENDPOINT

- Change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects

##### 9.7.1.1.2 SECONDARY ENDPOINTS

Change from baseline in: (revised per Amendment 02)

- Total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- The derived ADCOMS at 18 months of treatment in mild to moderate AD subjects (revised per Amendment 01)

#### 9.7.1.1.3 EXPLORATORY ENDPOINTS

(revised per Amendments 01 and 02)

Change from baseline in:

- The derived ADCOMS at 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
- Total hippocampal volume at 12 and 18 months of treatment in mild to moderate AD subjects as measured by vMRI
- CSF Aβ(1-x) and Aβ(1-42) after 4 weeks and 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ in MCI/Prodromal and mild to moderate AD subjects
- CSF biomarkers of neurodegeneration (eg, tau and p-tau) at 18 months of treatment in MCI/Prodromal and mild moderate AD subjects
- Plasma and CSF amyloid, and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild moderate AD subjects
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months in MCI/Prodromal and mild to moderate AD subjects as measured by vMRI
- Brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- The population PK parameters of E2609 including the effect of intrinsic and extrinsic factors (including *NAT2* phenotype) in MCI/Prodromal and mild to moderate AD subjects

### 9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol (PP) Analysis Set is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.

- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

#### 9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: The number (percent) of randomized and treated subjects who completed the study and who withdrew from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and withdrew from the study. The primary reasons for discontinuation from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

Completion of Study Treatment: The number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for discontinuation from the study drug are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, inadequate therapeutic response, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

#### 9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, MMSE and FAQ; categorical variables include sex, age group (≤65 years, age >65 years), race, ethnicity, *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal AD or mild to moderate AD). (revised per Amendment 01)

#### 9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up period will also be recorded.

#### 9.7.1.6 Efficacy Analyses

***The MCI/Prodromal Cohort***

The study in the MCI/Prodromal cohort is based on Bayesian adaptive design. Frequent interim analyses will be performed to assess the probability of early success and futility and to make early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis. Key definitions relevant to the Bayesian aspects of the adaptive design are given below.

**Study Definitions**

- **Maximum Effective Dose ($d_{Max}$):** The dose that achieves the greatest treatment effect.
- **$ED_{90}$:** The lowest dose that achieves at least 90% of the $d_{Max}$ treatment effect in the derived ADCOMS.
- **Early Success:** The study in the MCI/Prodromal cohort will meet early success criteria if the probability that the $ED_{90}$ at 18 months of treatment achieves 25% improvement over placebo is at least 80%. Early success is achieved before all MCI/Prodromal subjects complete 18 months of treatment and can only be determined after at least 200 MCI/Prodromal subjects have been randomized. If early success is declared before full randomization, the randomization of new MCI/Prodromal subjects will stop but subjects already randomized into the study will receive the full 18 months of treatment (following confirmation from the Sponsor's Senior Management).
- **Futility:** The study in the MCI/Prodromal cohort will meet statistical futility criteria if the probability that the $ED_{90}$ is better than placebo by the clinically significant difference of 25% is less than 5% at 18 months of treatment. The statistical futility boundary is binding; if the statistical futility boundary is crossed the study will be considered to have failed.

- **Study Success:** The study in the MCI/Prodromal cohort will be considered a success if an $ED_{90}$ at 18 months treatment has at least an 80% probability of achieving 25% improvement over placebo at either an interim analysis or at the final analysis.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

All mild to moderate AD subjects will be included in the efficacy evaluations of the Mild to Moderate AD cohort. The analysis of the Mild to Moderate AD cohort is based on the group sequential design. Interim analyses in the Mild to Moderate AD cohort will only be performed after the MCI/Prodromal cohort crosses the early success boundary. The early efficacy signal based on the change from baseline of ADCOMS at 18 months is defined as crossing the interim-analysis boundaries for overwhelming efficacy in the mild to moderate AD population. The O'Brien-Fleming (OF) boundaries based on Lan-DeMets alpha spending function will be used to assess overwhelming efficacy. The corresponding OF boundaries based on *P* values will be 0.076, 0.0221, and 0.0423 for the first, second, and final analyses, respectively, according to 2 planned interim analyses at the 60% and 80% information fraction. (revised per Amendment 01)

#### 9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

***Primary analysis of primary endpoint***

The primary analysis will be based on MCI/Prodromal subjects from the FAS with the prespecified censoring rule applied. The primary endpoint is the change from baseline to 18 months in the derived ADCOMS. The dose-response of the primary endpoint is modelled with a first-order normal dynamic linear model, where Normal and Inverse-Gamma priors are used. The primary efficacy analysis will calculate the Bayesian posterior probability that the dose identified is the most likely $ED_{90}$ dose that achieves 25% improvement over the placebo arm. At each interim analysis and the final analysis, 2 Bayesian probabilities will be summarized for each active dose: the probability it is the $ED_{90}$ dose and the probability of achieving 25% improvement over the placebo arm.

For the clinical efficacy data (ie, derived ADCOMS, MMSE, CDR, ADAS-cog, CBB, ISLT, and FAQ) subjects will be censored at the time of initiation of treatment with AChEIs or memantine, if they were not on these medications at the time of Baseline cognitive assessment (Visit 2), and will be censored at the time of dose adjustment of AChEIs or memantine if they were already on stable treatment with these medications at the time of Baseline cognitive assessment (Visit 2). The value of the primary endpoint for censored subjects will be imputed using data up to the censoring time and Bayesian longitudinal modeling.

***Sensitivity analysis of primary endpoint***

After unblinding, the primary endpoint will be analyzed using the Bayesian methods described above as well as conventional statistical methods. The following additional Bayesian analyses will be conducted as sensitivity analyses:

- The primary endpoint will be analyzed regardless of initiation of treatment, or dose adjustment, with AChEIs or memantine using the same Bayesian analysis method as primary analysis. This is an intent-to-treat analysis without any censoring.
- In case of early success, the primary analysis as well as the above sensitivity analyses will be repeated after all subjects have completed 18 months of treatment or have been lost to follow-up.

Statistical methods for the final conventional analyses will use a mixed-effects model with repeated measures (MMRM) on the change from baseline in the derived ADCOMS at 18 months. The model will include treatment groups, randomization stratification variables (the presence or absence of ongoing treatment with AChEIs or memantine or both, and *ApoE4* status), and baseline ADCOMS as covariates. Other covariates such as adjusted hippocampal volume will be studied. These analyses will be performed as sensitivity analyses on the FAS as well as the PP set and as such, no multiplicity adjustments will be made to account for the interim analyses. In case of early success, the conventional analyses will also be performed using the data collected before the interim analysis.

#### 9.7.1.6.2 SECONDARY EFFICACY ANALYSES

***The MCI/Prodromal Cohort***

An MMRM will be used to analyze the following secondary endpoint: (revised per Amendment 02)

- Change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI

Comparisons between each treatment group and placebo will be performed.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

The MMRM will be used to analyze the change from baseline of derived ADCOMS at 18 months in mild to moderate AD. If there is no treatment group-by-population interaction in the overall study, the MMRM analysis will include all subjects (MCI/Prodromal or mild to moderate AD) in the overall study. Otherwise, the MMRM analysis will only include subjects in the Mild to Moderate AD cohort. The comparison between placebo and active doses will be performed within mild to moderate AD subjects regardless of subjects included in the MMRM analysis. Dunnett's method will be used to control for multiplicity due to multiple comparisons.

#### 9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

(revised per Amendments 01 and 02)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in the derived ADCOMS at 12 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in total hippocampal atrophy at 12 and 18 months in mild to moderate AD subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) after 4 weeks and 18 months in MCI/Prodromal and mild to moderate AD subjects. Data from early discontinuations will also be included.
- Change from baseline in the clinical assessments: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in plasma and CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and 18 months as measured by vMRI in MCI/Prodromal and mild to moderate AD subjects

A linear mixed-model will be used to analyze the following exploratory endpoints:

- Change from baseline in brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in CSF biomarkers of neurodegeneration (eg, tau, p-tau) at 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects

Data from early discontinuations will also be used as appropriate. Comparisons between each treatment group and placebo will be performed.

A linear mixed-model with repeated measures will be used to determine the relationship between the following endpoints:

- Change from baseline in the derived ADCOMS score and the change from baseline in biomarkers in CSF at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in the derived ADCOMS score and change from baseline in imaging biomarkers (hippocampal, whole brain, and total ventricular volumes) at 12 and 18 months in MCI/Prodromal and mild to moderate AD subjects

*ApoE* status for heterozygous and homozygous E4 carriers will be included in the model to assess the effect of *ApoE* status in this relationship.

#### 9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

##### 9.7.1.7.1 PHARMACOKINETIC ANALYSES

The Safety Analysis Set will be used for individual E2609 concentration listings. The PK Analysis Set will be used for summaries of E2609 concentrations.

##### 9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Pharmacodynamic, PGx, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate statistical analysis plan. Please also refer to Appendix 3.

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). CSF Aβ(1-x), Aβ(1-42), t-tau, p-tau, and BACE1 will be assessed and data will be presented graphically. Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status.

Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels and exposure to E2609 in CSF will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. The PK/PD relationship between plasma PK parameters with other biomarkers may also be explored using similar methods.

Additionally, the relationship between plasma and CSF exposure to E2609 and the derived ADCOMS at 18 months, and the relationship between plasma and CSF exposure to E2609 and the change from baseline for 18 months in the ADAS-cog, the CDR, and the MMSE, will be explored graphically. Any emergent relationship will be explored through population PK/PD modeling.

Exposure-safety analyses may also be conducted.

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. The genomic DNA samples may also be stored and used as

described in Section 9.7.1.7.2. Details of PGx testing may be provided and reported separately.

#### 9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, and vital sign measurements will be summarized by treatment group using descriptive statistics.

##### 9.7.1.8.1 Extent of Exposure

The extent of exposure to study drug will be summarized as cumulative extent of exposure in 3-month intervals. The number and percent of subjects will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics in 3-month intervals. The number and percent of subjects will be presented by treatment group.

##### 9.7.1.8.2 Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 17.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and preferred term. A subject will be counted only once within an SOC and preferred term, even if the subject experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with

TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and preferred term. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

Adverse events will be summarized by the following subgroups: *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal or mild to moderate AD). (revised per Amendment 01)

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

#### 9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

Lymphocyte subsets (ie, CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages]) and regulatory T cells will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose.

Serum IgG, IgM, and IgA will be measured and summarized in the same manner as other laboratory parameters.

#### 9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

#### 9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to the end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 msec
- QTc interval >480 msec
- QTc interval >500 msec

Change from baseline in QTc interval:

- QTc interval increases from baseline >30 msec
- QTc interval increases from baseline >60 msec

#### 9.7.1.8.6 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog$_{14}$, MMSE, CDR, and CBB (see Section 9.7.1.6).

### 9.7.2 Determination of Sample Size

#### 9.7.2.1 Sample Size Rationale in the MCI/Prodromal Cohort

Primary endpoint – derived ADCOMS

The sample size and design characteristics to test the hypothesis for the primary objective based on the primary endpoint, change from baseline of the derived ADCOMS at 18 months, were determined by means of simulations. Extensive study simulations have shown that a total of 500 subjects will be sufficient to demonstrate that the most likely $ED_{90}$ dose achieves a 25% improvement over placebo with a probability of at least 80% in the interim and final analyses. There is at least a 90% probability of study success for the dose response scenarios where treatment was considered to have a clinically meaningful treatment effect. Simulations have also shown that if there is no obvious dose effect, the probability of falsely claiming superiority to placebo is at most 5%.

For each of the 4 treatment groups (3 active doses and placebo) the final number of subjects per group will differ depending on the observed interim treatment responses. The simulation plan will be an appendix to the statistical analysis plan and will present further details.

vMRI

The null hypothesis is that there is no difference between active dose and placebo. There are 3 null hypotheses corresponding to 3 active doses. The alternative hypothesis is that at least 1 null hypothesis is false (1-sided). The null hypotheses will be tested using Dunnett's method with 1-sided alpha of 0.05. The statistical power was estimated through simulation for a moderate dose-response assumption that the percent reduction in change from baseline of total hippocampal volume compared with placebo would be 15%, 20%, and 25% corresponding to the 3 doses, respectively. The estimated power for the actual planned study sample size is 78% at 18 months assuming an attrition rate of 20% at 18 months. Under a stronger dose-response assumption (ie, the percent reduction in change from baseline of total hippocampal volume compared with placebo is twice as much as that in the moderate dose-response assumption), the estimated power is at least 99% at 18 months.

Amyloid PET

The null and alternative hypotheses and the statistical test are the same as those for vMRI. To estimate the sample size for the amyloid PET imaging subgroup at 18 months, a common SD of the change from baseline was estimated at 0.33 and a reasonable mean difference between treatment and placebo was estimated as 0.25 (standardized uptake value ratio [SUVR]). Assuming a moderate dose-response, the best dose would achieve a difference of 0.25 (SUVR) and the middle and low doses would achieve a difference of 0.2 and 0.15 (SUVR), respectively; this would require a total of 100 subjects from all 4 arms at 18 months to achieve 80% power.

#### 9.7.2.2 Sample Size Rationale for the Mild to Moderate AD Cohort (revised per Amendment 01)

ADCOMS at Month 18

The null hypothesis is that there is no difference between active dose and placebo. There are 2 null hypotheses corresponding to 2 active doses. The alternative hypothesis is that at least 1 null hypothesis is false. The null hypotheses will be tested using Dunnett's test with 2-sided alpha of 0.05 as described for the Mild to Moderate AD cohort in Section 9.7.1.6.2. The statistical power was estimated through simulation for the dose-response assumption that the percent reduction in change from baseline of ADCOMS at 18 months compared with placebo would be 33% and 50% corresponding to the 2 doses, respectively. The estimated power for the actual planned 200 mild to moderate AD subjects is approximately 80% assuming a 2-sided alpha of 0.05. (revised per Amendment 01)

### 9.7.3 Interim Analysis

In order to make decisions about the remainder of the study as well as the full E2609 clinical development program, the sponsor will unblind safety, PK, and PD data on an ongoing basis and perform interim analyses of these data. Investigators, other clinical site staff, subjects and caregivers/informants will remain blinded to study treatment. (revised per Amendment 03)

An interim safety analysis will also be conducted when the first 60 subjects have completed 12 weeks of treatment (or discontinue study drug early) in Stage A. (revised per Amendments 01 and 03)

***The MCI/Prodromal Cohort***

The Bayesian interim analyses and response adaptive randomization will be conducted by an unblinded external independent analysis group in accordance with the protocol. Oversight of the Bayesian interim analyses and response adaptive randomization will be conducted by an independent unblinded committee that has expertise with Bayesian adaptive design in clinical studies to ensure that the response adaptive randomization process and interim analyses perform as expected. The analysis group will provide the interim analysis outcomes to the

committee at each interim analysis. The committee will ensure the integrity of the interim analysis and response adaptive randomization process through review of efficacy data. In addition, the committee will act in an independent advisory capacity to monitor the Bayesian interim analysis outcomes according to the early success and futility boundaries prespecified in the protocol. The committee will not be charged with any subject safety issues; this will remain the responsibility of the DSMB.

If the predefined early success criteria are met during the recruitment period, further recruitment and enrollment of MCI/Prodromal subjects into the study will stop (following confirmation from the Sponsor's Senior Management) and all currently randomized subjects will complete the full 18 months of treatment. No further interim analyses will be conducted after achieving early success.

If the predefined threshold for futility is reached, no additional subjects will be randomized into the study and the treatment of subjects already randomized into the study will stop and the study will be declared as "failed". All subjects will be monitored for safety for 3 months following their last dose.

If neither early success nor futility is reached and the study reaches full randomization, all subjects will complete 18 months of treatment. Interim efficacy analyses will be conducted every 3 months after full randomization is reached to assess futility and early success until all subjects complete 18 months of treatment. After full randomization, all study subjects will stop treatment only in the event of futility.

The DSMB will continue to monitor the safety aspects of the study throughout Stage A and Stage B. Details will be provided in the DSMB Charter. The study may be stopped for safety at any time.

The first Bayesian adaptive interim analysis will be conducted when 100 MCI/Prodromal subjects have been randomized into the study (ie, including MCI/Prodromal subjects from Stage A and Stage B). (revised per Amendment 01) Further interim efficacy analyses will be conducted after each additional 50 MCI/Prodromal subjects have been randomized, to a maximum of 500 MCI/Prodromal subjects (ie, at 100, 150, 200, 250, 300, 350, 400, 450, 500 subjects randomized). If the study reaches full randomization, additional interim analyses will be conducted every 3 months until all subjects complete 18 months of treatment. The study will be monitored for futility at each interim analysis. Starting at the interim analysis for 200 subjects, the study will be monitored for success at each interim analysis. Each interim analysis will be conducted on data for the derived ADCOMS.

In addition, at each interim efficacy analysis, response adaptive randomization will be used to update the allocation of new subjects between placebo and active doses according to a predefined automated algorithm.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

A group sequential design will be used for the Mild to Moderate AD cohort. (revised per Amendment 01) This design includes 3 looks, 2 interim looks (when 60% and 80% information fractions are achieved) and 1 final look. The information fraction is the number of assessments in all treatment arms divided by the total number of expected assessments. Interim analyses will be performed after the MCI/Prodromal cohort crosses the early success boundary. The corresponding efficacy boundaries will be 0.076, 0.022, and 0.0423 for the first, second, and final analyses, respectively. If the actual information fraction during the interim analyses is different from 60% or 80% at the interim, the efficacy boundaries will be adjusted based on the actual information fraction.

If early success in the MCI/Prodromal cohort is not achieved before the final analysis that is performed when all subjects have completed 18 months treatment, then only a final analysis will be performed in mild to moderate AD subjects. In the event of futility in the MCI/Prodromal cohort, an analysis will be performed for the Mild to Moderate AD cohort based on the data for mild to moderate AD subjects available at that time. (revised per Amendment 01)

Randomization into the Mild to Moderate AD cohort will remain at a fixed schedule throughout Stage B. (revised per Amendment 01)

The interim analyses in the Mild to Moderate AD cohort will be conducted by an independent analysis group. (revised per Amendment 01)

### 9.7.4 Other Statistical/Analytical Issues

**Adaptive Randomization in the MCI/Prodromal Cohort**

Randomization to placebo or 1 of 3 dose groups of E2609 will be fixed for the first 100 MCI/Prodromal subjects randomized in the study (1:1:1:1; placebo to each of the 3 active doses for the first 100 MCI/Prodromal subjects randomized, including those randomized from both Stage A and Stage B). Thereafter, randomization probabilities to each treatment group will be updated at each interim analysis, such that the randomization probability will be increased for the placebo group and dosage groups that represent the potential target dose ($ED_{90}$), and simultaneously decreased for other active arms. (revised per Amendment 01)

**Randomization in the Mild to Moderate AD Cohort** (revised per Amendment 01)

In Stage A, the mild to moderate AD subjects will be randomized to placebo or 1 of 3 E2609 dose groups (5, 15, and 50 mg of E2609) at a 1:1:1:1 ratio, while in Stage B, the mild to moderate AD subjects will be randomized to placebo or 1 of 2 E2609 dose groups (15 and 50 mg E2609) at a 1:1:1 ratio. (revised per Amendment 01)

**Stratification** (revised per Amendment 01)

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

### 9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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# 11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

## 11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

## 11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

## 11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

## 11.4 Recording of Data

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document, except when a section of the eCRF itself is used as the source document. Any correction to entries made on the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each eCRF. The investigator will report the eCRFs to the sponsor and retain a copy of the eCRFs.

## 11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents.

## 11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

## 11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

## 11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

## 11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

## 11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or CTA executed between the institution/investigator and the sponsor/CRO.

## 11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

## 11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

# 12 APPENDICES

## Appendix 1 Sponsor's Grading for Laboratory Values

(revised per Amendment 01)

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **BLOOD/BONE MARROW** | | | | |
| Hemoglobin (conversion from g/dL×0.6206) | **Female** (ULN=15.9 g/dL)<br><11.1 – 10.0 g/dL<br><111 – 100 g/L<br><6.9 – 6.2 mmol/L<br>**Male** (ULN=17.7 g/dL)<br><12.6 – 10.0 g/dL<br><126 – 100 g/L<br><7.8 – 6.2 mmol/L | <10.0 – 8.0 g/dL<br><100 – 80 g/L<br><6.2 – 4.9 mmol/L | <8.0 g/dL<br><80 g/L<br><4.9 mmol/L;<br>transfusion indicated | life-threatening consequences; urgent intervention indicated |
| Leukocytes (total white blood cell) | <3.40 – 3.0×$10^9$/L<br><3.40 $10^3$/uL – 3000/$mm^3$<br>(ULN=10.80 $10^3$/μL) | <3.0 – 2.0×$10^9$/L<br><3000 – 2000/$mm^3$ | <2.0 – 1.0×$10^9$/L<br><2000 – 1000/$mm^3$ | <1.0×$10^9$/L<br><1000/$mm^3$ |
| Lymphocytes | not applicable | <700 – 500/$mm^3$<br><0.7 – 0.5×$10^9$/L | <500 – 200/$mm^3$<br><0.5 – 0.2×$10^9$/L | <200/$mm^3$<br><0.2×$10^9$/L |
| Neutrophils | not applicable | <1.4 – 1.0×$10^9$/L<br><1400 – 1000/$mm^3$ | <1.0 – 0.5×$10^9$/L<br><1000 – 500/$mm^3$ | <0.5×$10^9$/L<br><500/$mm^3$ |
| Platelets | <155 – 75.0×$10^9$/L<br><155 $10^3$/uL – 75,000/$mm^3$<br>(ULN=379 $10^3$/μL) | <75.0 – 50.0×$10^9$/L<br><75,000 – 50,000/$mm^3$ | <50.0 – 25.0×$10^9$/L<br><50,000 – 25,000/$mm^3$ | <25.0×$10^9$/L<br><25,000/$mm^3$ |
| **METABOLIC/LABORATORY** | | | | |
| Albumin, serum- low (hypoalbuminemia) | **2 - 59 years** (ULN=5.5 g/dL)<br><3.5 – 3 g/dL<br><35 – 30 g/L<br>**59 -69 years** (LLN-ULN)<br><3.6 g/dL – 3 g/dL<br>**69 -79 years** (LLN-ULN)<br><3.5g/dL – 3g/dL<br>**79 -89 years** (LLN-ULN)<br><3.5g/dL – 3g/dL | <3 – 2 g/dL<br><30 – 20 g/L | <2 g/dL<br><20 g/L | life-threatening consequences; urgent intervention indicated |
| Alkaline phosphatase | **Female:**<br>**18 -19 years**<br>>101 – 3.0×101<br>**19 -61 years**<br>ULN=107<br>**61 -71 years**<br>ULN=112<br>**71 -150 years**<br>ULN=108<br>**Male**<br>**18 -19 years**<br>>127 – 3.0×127<br>**19 -61 years**<br>ULN=102<br>**61 -71 years**<br>ULN=103<br>**71 -150 years**<br>ULN=105 | >3.0 – 5.0×ULN<br>See previous column for ULN values | >5.0 – 20.0×ULN<br>See previous column for ULN values | >20.0×ULN<br>See previous column for ULN values |
| Alanine aminotransferase | **Female:**<br>>32 – 3.0×32<br>**Male:**<br>>44 – 3.0 x 44 | **Female:**<br>>3.0 – 5.0×32<br>**Male**<br>>3.0 – 5.0×44 | **Female:**<br>>5.0 – 20.0×32<br>**Male:**<br>>5.0 – 20.0×44 | **Female:**<br>>20.0×32<br>**Male:**<br>>20.0×44 |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Aspartate aminotransferase | >40 – 3.0×40 | >3.0 – 5.0×40 | >5.0 – 20.0×40 | >20.0×40 |
| Bilirubin (hyperbilirubinemia) | >1.2 – 1.5×1.2 | >1.5 – 3.0×1.2 | >3.0 – 10.0×1.2 | >10.0×1.2 |
| Calcium, serum-low (hypocalcemia) (conversion to mmol×0.25) | <8.5 – 8.0 mg/dL<br><2.13 – 2.0 mmol/L | <8.0 – 7.0 mg/dL<br><2.0 – 1.75 mmol/L | <7.0 – 6.0 mg/dL<br><1.75 – 1.5 mmol/L | <6.0 mg/dL<br><1.5 mmol/L |
| Calcium, serum-high (hypercalcemia) | >10.6 – 11.5 mg/dL<br>>2.65 – 2.9 mmol/L | >11.5 – 12.5 mg/dL<br>>2.9 – 3.1 mmol/L | >12.5 – 13.5 mg/dL<br>>3.1 – 3.4 mmol/L | >13.5 mg/dL<br>>3.4 mmol/L |
| Cholesterol, serum-high (hypercholesterolemia) (conversion to mmol/L ×0.02586) | **0 -19 years**<br>>169 – 300 mg/dL<br>>4.37 – 7.75 mmol/L<br>**19 -150 years**<br>>199 – 300 mg/dL<br>>5.15 – 7.75 mmol/L | >300 – 400 mg/dL<br>>7.75 – 10.34 mmol/L | >400 – 500 mg/dL<br>>10.34 – 12.92 mmol/L | >500 mg/dL<br>>12.92 mmol/L |
| Creatinine | **Female**<br>>1.00 mg/dL – 1.5×1.00<br>**Male**<br>>1.27 mg/dL – 1.5×1.27 | **Female**<br>>1.5 – 3.0×1.00<br>**Male**<br>>1.5 mg/dL – 3.0×1.27 | **Female**<br>>3.0 – 6.0×1.00<br>**Male**<br>>3.0 mg/dL – 6.0 ×1.27 | **Female**<br>>6.0×1.00<br>**Male**<br>>6.0×1.27 |
| Gamma glutamyl transpeptidase | **Female**<br>>60 IU/L – 3.0×60<br>**Male**<br>>65 IU/L – 3.0×65 | **Female**<br>>3.0 – 5.0×60<br>**Male**<br>>3.0 – 5.0×65 | **Female**<br>>5.0 – 20.0×60<br>**Male**<br>>5.0 – 20.0×65 | **Female**<br>>20.0×60<br>**Male**<br>>20.0×65 |
| Glucose, serum-high (hyperglycemia) (conversion to mmol/L ×0.0555) | **Fasting glucose value**<br>>99 – 160 mg/dL<br>>5.5 – 8.9 mmol/L | **Fasting glucose value**<br>>160 – 250 mg/dL<br>>8.9 – 13.9 mmol/L | >250 – 500 mg/dL;<br>>13.9 – 27.8 mmol/L;<br>hospitalization indicated | >500 mg/dL;<br>>27.8 mmol/L;<br>life-threatening consequences |
| Glucose, serum-low (hypoglycemia) | <65 – 55 mg/dL<br><3.6 – 3.0 mmol/L | <55 – 40 mg/dL<br><3.0 – 2.2 mmol/L | <40 – 30 mg/dL<br><2.2 – 1.7 mmol/L | <30 mg/dL<br><1.7 mmol/L<br>life-threatening consequences;<br>seizures |
| Phosphate, serum-low (hypophosphatemia) (conversion to mmol/L ×0.323) | not applicable | <2.5 – 2.0 mg/dL<br><0.8 – 0.6 mmol/L | <2.0 – 1.0 mg/dL<br><0.6 – 0.3 mmol/L | <1.0 mg/dL<br><0.3 mmol/L<br>life-threatening consequences |
| Potassium, serum-high (hyperkalemia) | not applicable | >5.5 – 6.0 mmol/L | >6.0 – 7.0 mmol/L<br>hospitalization indicated | >7.0 mmol/L<br>life-threatening consequences |
| Potassium, serum-low (hypokalemia) | <3.5 mEq/L – 3.0 mmol/L | <LLN – 3.0 mmol/L;<br>symptomatic; intervention indicated | <3.0 – 2.5 mmol/L<br>hospitalization indicated | <2.5 mmol/L<br>life-threatening consequences |
| Sodium, serum-high (hypernatremia) | >144 mEq/L – 150 mmol/L | >150 – 155 mmol/L | >155 – 160 mmol/L<br>hospitalization indicated | >160 mmol/L<br>life-threatening consequences |
| Sodium, serum-low (hyponatremia) | <134 mEq/L – 130 mmol/L | Not applicable | <130 – 120 mmol/L | <120 mmol/L<br>life-threatening consequences |
| Triglyceride, serum-high (hypertriglyceridemia) | 150 – 300 mg/dL<br>1.71 – 3.42 mmol/L | >300 – 500 mg/dL<br>>3.42 – 5.7 mmol/L | >500 – 1000 mg/dL<br>>5.7 – 11.4 mmol/L | >1000 mg/dL<br>>11.4 mmol/L<br>life-threatening consequences |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Uric acid, serum-high (hyperuricemia) | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | Not applicable | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | >10 mg/dL<br>>0.59 mmol/L<br>life-threatening consequences |

LLN = lower limit of normal, ULN = upper limit of normal.

# Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, Listing 3, Listing 4, Listing 5, and Listing 6. Medications permitted with restrictions are listed in Listing 7, Listing 8, and Listing 9. **These may not be all-inclusive listings.** Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-202 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 9 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

## Prohibited Prior/Concomitant Medications

### Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Prohibited from 14 days (or 5 half-lives, whichever is longer) before Randomization until after the last treatment visit** | | |
| **Anti-arrhythmic/ abnormal heart rhythm** | | |
| Amiodarone | Cordarone; Pacerone | Incidence in females greater than males, Torsades de Pointes risk regarded as low |
| Disopyramide | Norpace | Incidence in females greater than males |
| Dofetillide | Tikosyn | |
| Ibutilide | Corvert | Incidence in females greater than males |
| Procainamide | Pronestyl; Procan | |
| Quinidine | Cardioquin; Quinaglute | Incidence in females greater than males |
| Sotalol | Betapace | Incidence in females greater than males |
| **Antihistamine/ allergic rhinitis** | | |
| Astemizole | Hismanal | No longer available in United States |
| Terfenadine | Seldane | No longer available in United States |
| **Anti-anginal/ heart pain** | | |
| Bepridil | Vascor | Incidence in females greater than males |
| **Antibiotic/ bacterial infection** | | |
| Clarithromycin | Blaxin | |
| Moxifloxacin | Avelox | |
| Sparfloxadin | Zagam | |
| **Listing 1 continued** | | |
| **Antimalarial/ malaria infection** | | |
| Chloroquine | Aralen | |
| Halofantrine | Halfan | Incidence in females greater than males |
| **Antipsychotic/ anti-emetic/ schizophrenia/ nausea** | | |
| Chloropromazine | Thorazine | |
| **Gastrointestinal stimulant/ heartburn** | | |
| Cisapride | Propulsid | |
| **Antinausea/ nausea** | | |

## Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| Domperidone | Motillum | Not available in the United States |
| **Sedative; antinausea/ anesthesia adjunct, nausea** | | |
| Droperidol | Inapsine | |
| **Antibiotic; gastrointestinal stimulant/ bacterial infection; increase gastrointestinal motility** | | |
| Erythromycin | Erythrocin; E.E.S. | Incidence in females greater than males |
| **Antipsychotic/ schizophrenia** | | |
| Haloperidol | Haldol | When given intravenously or at higher than recommended doses, risk of sudden death, QT prolongation, and torsades increases |
| Mesoridazine | Serentil | |
| Thioridazine | Mellaril | |
| **Opiate agonist/ pain control, narcotic dependence** | | |
| Levomethadyl | Orlaam | |
| Methadone | Methadose; Dolophine | Incidence in females greater than males |
| **Anti-infective/ pneumocystis pneumonia** | | |
| Pentamidine | Pentam; NebuPent | Incidence in females greater than males |
| **Antipsychotic/ Tourette's tics** | | |
| Pimozide | Orap | Incidence in females greater than males |
| **Antilipemic/ hypercholesterolemia** | | |
| Probucol | Lorelco | No longer available in United States |
| **Anticancer** | | |
| Arsenic trioxide | Trisenox | Used for leukemia |
| Vandetanib | Zactima | Used for thyroid cancer |

Note: This list is not exhaustive.
QTc = Corrected QT interval.

## Listing 2 Prohibited Medications Within 7 Days (or 5 Half-lives, Whichever is Longer) Before Randomization and Until after the Last Treatment Visit)

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Anticoagulants** | |
| Adeporin | Normiflo |
| Alteplase, tPA | Activase, Cathflo Activase |
| Anisindione | Miradon |
| Antithrombin III | ATryn, Thrombate III |
| Argatroban | Argatroban |
| Bivalirudin | Angiomax |
| Dabigatran | Pradaxa |
| Dalteparin | Fragmin |
| Danaparoid | Orgaran |
| Dicumarol | Dicumarol |
| Enoxaparin | Lovenox |
| Fondaparinux | Arixtra |
| Heparin Sodium | Monoject |
| Lanoteplase | Lanoplase |
| Lepirudin | Refludan |
| Pentosan polysulfate sodium | Elmiron |
| Reteplase | Retavase, Retevase |
| Staphylokinase | Eskinase, Heberkinasa Kabikinase, Streptase, Thrombosolv, Zykinase |
| Streptokinase | Streptase |
| Tenecteplase | TNKase |
| Tinzaparin | Innohep |
| Urokinase | Abbokinase, Kinlytic |
| Warfarin | Coumadin, Jantoven |
| **Antiplatelet drugs** | |
| Aspirin and Plavix (revised per Amendment 01) | For subjects who consent to CSF sample collection: Aspirin or clopidogrel is permitted in all subjects. Aspirin and clopidogrel in combination is not permitted. (revised per Amendments 01 and 02)<br>For subjects who do not consent to CSF sample collection: Aspirin and clopidogrel, individually or in combination, is permitted. (revised per Amendment 02) |

Note: This list is not exhaustive.

## Listing 3 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Randomization and Until after the Last Treatment Visit

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Systemic Immunosuppressants[a] and Immunomodulatory therapy** | |
| Azathioprine | Azasan, Imur |
| Ciclosporine | Gengraf, Neoral |
| Dexamethasone | Decadron, Dexasone, Diodex, Hexadrol, Maxidex |
| Fingolimod | Gilenya |
| Methotrexate | Trexall |
| Methylprednisolone | Medrol, Meprolone |
| Mycophenolate | CellCept, Myfortic |
| Prednisolone | Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS |

Note: This list is not exhaustive.

a: Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

## Listing 4 Prohibited Medications Within 6 Months Before Randomization

| **Generic name** | **Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™)** |
|---|---|
| **Immunoglobulin therapy** | |
| Adalimumab | Humira |
| Bevacizumab | Avastin |
| Efalizumab | Raptiva |
| Etanercept | Enbrel |
| Immune globulin IV, IVIG, IGIV | Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S |
| Infliximab | Remicade |
| Omalizumab | Xolair |
| Ranibizumab | Lucentis |
| Other monoclonal antibodies not listed here | |

Note: This list is not exhaustive.

### Listing 5 Prohibited Live Vaccines Within 3 Months Before Randomization Until after the Last Treatment Visit (this does not apply to non-live/inactivated vaccines)

| **Bacterial vaccines** | **Viral vaccines** |
|---|---|
| Bacillus Calmette-Guérin vaccine against tuberculosis | Measles vaccination |
| Cholera vaccination (oral) | Rubella vaccination |
| | Oral polio vaccination (Sabin) |
| | Yellow fever vaccination |
| | Varicella (chickenpox) vaccination |
| | Rotavirus vaccination |
| | Japanese encephalitis vaccination |
| | Live attenuated influenza vaccine (FluMist, Fluenz) |
| Typhoid vaccination (oral) | Mumps vaccination |

Note: This list is not exhaustive

## Listing 6 Strong CYP3A4 Inhibitors Prohibited Within 5 Half-Lives or 14 Days (Whichever Is Longer) Before Randomization Until After the Last Treatment Visit

| Generic name | Brand name(s) |
|---|---|
| boceprevir | Victrelis |
| clarithromycin | Clarithromycin, clarithromycin extended release, Prevpac |
| cobicistat | Tybost, Stribild, |
| conivaptan | Vaprisol |
| danoprevir | |
| elvitegravir | Vitekta, Stribild |
| indinavir | Crixivan |
| itraconazole | Sporanoz, Onmel |
| ketoconazole | Xolegel, Nizoral, Ketodan |
| lopinavir | Kaletra |
| nefazodone | Serzone |
| nelfinavir | Viracept |
| posaconazole | Noxafil |
| ritonavir | Norvir, Kaletra |
| saquinavir | Invirase, Fortovase |
| telaprevir | Incivek |
| telithromycin | Ketek |
| tipranavir | Aptivus |
| troleandomycin | Triocetin |
| voriconazole | Vfend, Voriconazole |

Note: This list is not exhaustive

## Permitted Prior/Concomitant Medications

### Listing 7 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Baseline Cognitive Assessments at Visit 2 and Remain on the Same Stable Dose from Baseline to Follow-Up Visit 2

| **Generic name** | **Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™)** |
|---|---|
| **Cognitive Enhancers** | |
| Donepezil | Aricept |
| Galantamine | Reminyl |
| Memantine | Namenda |
| Rivastigmine | Exelon |

Note: This list is not exhaustive.

## Listing 8 Permitted Medications Used on PRN Basis Which are Not to be Used Within 72 Hours before Cognitive Testing

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Opiates** | |
| Morphine | Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol |
| **Opiate Agonists** | |
| Codeine | Codeine |
| Fentanyl | Actiq, Duragesic, Fentora, Onsolis, Sublimaze |
| Meperidine | Demerol, Meperitab |
| Oxycodone | Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol |
| Other opioids or opioid agonists which are used on PRN basis | |
| **Benzodiazepines and sedatives** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Amitriptyline | (various) |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Dothiepin | (various) |
| Estazolam | ProSom |
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |
| Lorazepam | Ativan |
| Midazolam | Versed |
| Olanzapine | Zyprexa |
| Promethazine | Phenergan; others |
| Ramelteon | Rozerem |
| Risperidone | Risperdal |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zolpidem | Ambien; others |
| Zopiclone | (various) |
| Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives | |

Note: This list is not exhaustive

PRN = Pro re nata

## Listing 9 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| If to be used on a PRN basis see Listing 8. If to be used chronically, subjects must be on a stable dose for ≥4 weeks before Baseline. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks. | |
| **Antidepressants** | |
| Amitriptyline hydrochloride | Elavil |
| Amoxapine | Amoxapine |
| Bupropion | Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin |
| Citalopram | Celexa |
| Clomipramine hydrochloride | Anafranil |
| Desipramine hydrochloride | Norpramin |
| Desvenlafaxine | Pristiq |
| Doxepin hydrochloride | Prudoxin, Silenor, Sinequan, Zonalon |
| Duloxetine | Cymbalta |
| Escitalopram | Lexapro |
| Fluoxetine | Prozac, Sarafem, Selfemra |
| Fluvoxamine | Luvox |
| Imipramine hydrochloride | Tofranil |
| Isocarboxazid | Marplan |
| Maprotiline hydrochloride | Ludiomil |
| Mirtazapine | Remeron Soltab |
| Nortriptyline hydrochloride | Aventyl, Pamelor |
| Paroxetine | Paxil, Pexeva |
| Phenelzine | Nardil |
| Protriptyline hydrochloride | Vivactil |
| Rasagiline | Azilect |
| Selegiline | EMSAM |
| Sertraline | Sertaraline, Zoloft |
| Tranylcypromine | Parnate |
| Trazodone hydrochloride | Desyrel, Oleptro |
| Trimipramine maleate | Surmontil |
| Venlafaxine hydrochloride | Effexor |

## Listing 9 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Mood Stabilizers (Listing 8 continued)** | |
| Carbamazepine | Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR |
| Lamotrigine | Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR |
| Valproic acid | Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate |
| **Antipsychotics** | |
| Acetophenazine | Tindal |
| Aripiprazole | Abilify |
| Asenapine | Saphris |
| Olanzapine | Zyprexa |
| Chlorpromazine | Thorazine |
| Haloperidol | Haloperidol, Haldol |
| Clozapine | Clozaril, Fazaclo |
| Fluphenazine | Prolixin |
| L-Methylfolate | Deplin, L-Methylfolate Calcium |
| Loxapine | Loxitane |
| Mesoridazine | Serentil |
| Perphenazine | Trilafon |
| Quetiapine | Seroquel |
| Risperidone | Risperdal |
| Thioridazine | Mellaril |
| Thiothixene | Navane |
| Trifluoperazine | Stelazine |
| **Benzodiazepines** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Estazolam | ProSom |
| Flunitrazepam | Rohypnol |

## Listing 9 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| Flurazepam | Dalmane |
| Lorazepam | Ativan |
| Midazolam | Versed |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zopiclone | Imovane, Zimovane |
| Zopidem | Ambien, Ambien CR, Intermezzo, Stilnox, Stilnoct, Sublinox, Hypnogen, Zolsana |

Note: This list is not exhaustive.

PRN = Pro re nata

# Appendix 3 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

## Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

## Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In

this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

### Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

### Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed

scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

# Appendix 4 AEs Indicating Signals of Possible Drug Abuse Potential

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| 1 | **Euphoric mood** | Euphoric mood |
| | | Euphoria |
| | | Euphoric |
| | | Exaggerated well-being |
| | | Excitement excessive |
| | | Feeling high |
| | | Felt high |
| | | High |
| | | High feeling |
| | | Laughter |
| 2 | **Elevated mood** | Elevated mood |
| | | Mood elevated |
| | | Elation |
| 3 | **Feeling abnormal** | Feeling abnormal |
| | | Cotton wool in head |
| | | Feeling dazed |
| | | Feeling floating |
| | | Feeling strange |
| | | Feeling weightless |
| | | Felt like a zombie |
| | | Floating feeling |
| | | Foggy feeling in head |
| | | Funny episode |
| | | Fuzzy |
| | | Fuzzy head |
| | | Muzzy head |
| | | Spaced out |
| | | Unstable feeling |
| | | Weird feeling |
| | | Spacey |
| 4 | **Feeling drunk** | Feeling drunk |
| | | Drunkenness feeling of |
| | | Drunk-like effect |
| | | Intoxicated |
| | | Stoned |
| | | Drugged |
| 5 | **Feeling of relaxation** | Feeling of relaxation |
| | | Feeling relaxed |
| | | Relaxation |
| | | Relaxed |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Increased well-being |
| | | Excessive happiness |
| **6** | **Thinking abnormal** | Thinking abnormal |
| | | Abnormal thinking |
| | | Thinking irrational |
| | | Thinking disturbance |
| | | Thought blocking |
| | | Wandering thoughts |
| **7** | **Hallucination** | Hallucination |
| | | Illusions |
| | | Flashbacks |
| | | Floating |
| | | Rush |
| | | Feeling addicted |
| **8** | **Inappropriate affect** | Elation inappropriate |
| | | Exhilaration inappropriate |
| | | Feeling happy inappropriately |
| | | Inappropriate affect |
| | | Inappropriate elation |
| | | Inappropriate laughter |
| | | Inappropriate mood elevation |
| **9** | **Mood disorders and disturbances** | Mental disturbance |
| | | Depersonalisation |
| | | Psychomotor stimulation |
| | | Mood disorders |
| | | Emotional and mood disturbances |
| | | Delirium |
| | | Delirious |
| | | Mood altered |
| | | Mood alterations |
| | | Mood instability |
| | | Mood swings |
| | | Emotional lability |
| | | Emotional disorder |
| | | Emotional distress |
| | | Personality disorder |
| | | Impatience |
| | | Abnormal behavior |
| | | Delusional disorder |
| | | Irritability |
| **10** | **Drug tolerance** | Drug tolerance |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Habituation |
| | | Drug withdrawal syndrome |
| | | Substance-related disorders |
| **11** | **Psychosis** | Psychosis |
| | | Psychotic episode or disorder |
| **12** | **Dissociative State** | Dissociation |
| | | Disconnected |
| | | Derealisation |
| | | Depersonalisation |
| | | Detached |
| | | Sensation of distance from one's environment |
| | | Loss of a sense of personal identity |

# Appendix 5 Eisai Lymphocyte Subset Criteria for Study E2609-G000-202: Justification for a Population-Adjusted Approach

**Introduction:**

The Eisai clinical study, E2609-G000-202, requires the analysis of absolute numbers of various functional subsets of circulating lymphocytes. These are distinguished by identification of various complementary differentiation (CD) markers on the cell surface using fluorescent-labeled antibody reagents and flow cytometry. Current enumeration of certain lymphocyte subsets form part of the immunologically based eligibility criteria for study enrollment, as well as being monitored for safety for enrolled and treatment randomized subjects. The Trucount™ M (Becton, Dickinson and Company [BD], BD Biosciences, San Jose, CA) antibody reagents used for the lymphocyte subset eligibility criteria, provides readouts for both absolute (BD Trucount tubes) and percentage of lymphocyte subsets, and includes the following CD markers: CD3 (T cells), CD4 (T helper cells), CD8 (cytotoxic T cells), CD16/56 (natural killer cells), CD14 (macrophages), and CD19 (B cells).

Trucount lymphocyte subset reference ranges provided by the reagent manufacturer (BD) for both absolute and percentages were established for clinical use as an in vitro diagnostic using standardized reference interval methodology. These LLN for the various lymphocyte subsets are currently being used by the central laboratory for Eisai Study E2609-G000-202 to determine eligibility of screened subjects and as part of safety assessments during post-randomization visits. The eligibility criterion excludes subjects with absolute counts of T and B cell markers (CD4, CD8, and CD19 respectively) less than the reference range lower limit of normal (<LLN) at Screening or Baseline.

**Need to assign age appropriate reference ranges:**

Reference ranges established by the vendor according to working group guidance[3] may not be representative of different subgroup analyses (eg, ancestry, disease state, age, gender, etc.), and therefore interval adjustment may be required depending on the subpopulation of interest. The working group guidance for reference intervals (CLSI, 2010[4]) recommends examining data to determine if >10% of subjects are outliers (ie, more than 10% < LLN), and if so, to initiate development of subgroup-appropriate intervals by analyzing data from the literature or internal studies representing the reference population [a minimum of 120 observations recommended by the guidance.[3]]

Data from the ongoing Study E2609-G000-202 has been examined and greater than 10% of the study population screening samples fall below the manufacturer recommended LLN for the key lymphocyte subsets. The population for Study E2609-G000-202 are patients aged 50 to 85 years old inclusive with Mild Cognitive Impairment due to AD or with Mild to Moderate dementia due to AD. Lymphocyte subset data from a data cut of 93 screened subjects was analyzed and showed that both CD8 and CD4 had greater than 10% of the

subjects with results <LLN (26.9%, <220 cells/mm$^3$ and 13%, <404 cells/mm$^3$, respectively); CD19 had approximately 10% of the subjects with results <LLN (9.7%, <80 cells/mm$^3$).

To further determine if the outlier data observations from the ongoing Study E2609-G000-202 were associated with disease status or age, lymphocyte subset data from additional Eisai studies that included healthy elderly subjects or patients diagnosed with MCI or mild/moderate AD were examined. The individuals from all 3 studies included the same 50-to 85-year-old age range as the current E2609-G000-202 study. The studies evaluated include: (1) Study E2609-A001-002 treatment study (n=50 healthy elderly); (2) Lymphocyte subset pilot study in healthy elderly [n=30]; and (3) Lymphocyte subset pilot study in AD/MCI [n=31]. Screening or baseline sample from all 4 studies had >10% of the CD8 absolute counts below reference LLN, 2 out of 4 had >10% of the CD19 absolute counts below reference LLN and 1 out of 4 had >10% of the CD4 absolute counts out of reference LLN [Table 10, Table 11, and Table 12]. The data suggests that the reference values of LLN for CD4, CD8, and CD19 subsets are not a disease-associated observation but are related to the age of the study population being evaluated.

In addition to the Eisai study data, age related decline in lymphocyte subsets has been described in the literature Yan et.al.[1][2] Analysis was performed using flow cytometry on peripheral blood leukocytes using healthy subjects across the 3rd and 10th decades of life. The results from the Yan study (n=80; 37 males, 43 females) demonstrated that with advancing age there was a significant decline in the percentage of lymphocytes, specifically naive T cells [CD3 *P*=0.03], cytotoxic T cells [CD8 *P*=0.08] and activated B cells [CD20/CD69 *P*=0.03] with certain subsets demonstrating even greater decline in males.[1] The age associated changes in immune capabilities, termed "immunosenescence", which include degenerative changes in the lymph nodes, effects on lymphocyte subsets and changes in adaptive immunity may underlie the increased risk of infection and cancer and decreased immune function in the elderly. This, along with the data from the four Eisai studies described earlier, support the readjustment of the LLNs for the CD reference ranges used for eligibility in Study E2609-G000-202 such that they are better suited to the older patient population enrolling in this study which is thought to be representative of the wider patient population.

**Determining the new LLN criteria:**

The recommended method for establishing reference intervals is the nonparametric approach where the underlying distribution of the data does not matter. The values received from the data (a minimum of 120 observations representing the subgroup population of interest is recommended) are rank ordered and can be used to evaluate the comparative reference interval.[3]

When data from the 4 Eisai studies are put in rank order (see Table 10, Table 11, and Table **12**), and a 10% cut value is applied to each of the 3 CD markers of interest the following age-adjusted LLN values are generated:

**Table 9 Summary of CD4, CD8, and CD19 LLNs and Age-Adjusted LLNs**

| Lymphocyte Subset | Current LLN | Age-adjusted LLN |
|---|---|---|
| CD4 absolute count | 404 cells/$mm^3$ | 396 cells/$mm^3$ |
| CD8 absolute count | 220 cells/$mm^3$ | 157 cells/$mm^3$ |
| CD19 absolute count | 80 cells/$mm^3$ | 74 cells/$mm^3$ |

**Table 10 Summary of CD Counts (Parameter: CD19)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 30 | 203 |
| Mean | 213.47 | 198.49 | 159.20 | 172.77 | 192.57 |
| Median | 189.66 | 163.00 | 118.50 | 159.50 | 164.86 |
| 5th percentile | 84.81 | 59.00 | 38.00 | 69.00 | 59.00 |
| 10th percentile | 102.26 | 81.00 | 42.00 | 70.50 | 74.00 |
| 25th percentile | 139.66 | 104.00 | 75.00 | 100.00 | 104.58 |
| 75th percentile | 261.51 | 225.00 | 225.00 | 246.00 | 246.00 |
| 95th percentile | 376.67 | 443.00 | 424.00 | 384.00 | 402.00 |
| Range | 66.19, 593.48 | 17.00, 1066.00 | 37.00, 455.00 | 39.00, 415.00 | 17.00, 1066.00 |

**Table 11 Summary of CD Counts (Parameter: CD8)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 31 | 204 |
| Mean | 362.72 | 352.18 | 324.63 | 427.74 | 362.20 |
| Median | 364.74 | 330.00 | 344.00 | 315.00 | 336.39 |
| 5th percentile | 115.02 | 138.00 | 86.00 | 100.00 | 115.02 |
| 10th percentile | 170.24 | 151.00 | 159.50 | 153.00 | 157.00 |
| 25th percentile | 253.37 | 213.00 | 204.00 | 217.00 | 230.00 |
| 75th percentile | 465.52 | 425.00 | 405.00 | 494.00 | 438.00 |
| 95th percentile | 614.57 | 716.00 | 557.00 | 988.00 | 702.00 |
| Range | 98.45, 702.50 | 37.00, 803.00 | 61.00, 702.00 | 54.00, 2255.00 | 37.00, 2255.00 |

**Table 12 Summary of CD Counts (Parameter: CD4)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 31 | 204 |
| Mean | 846.15 | 839.58 | 789.27 | 804.52 | 828.46 |
| Median | 836.94 | 805.00 | 777.50 | 771.00 | 791.50 |
| 5th percentile | 388.44 | 337.00 | 395.00 | 351.00 | 344.00 |
| 10th percentile | 479.55 | 361.00 | 490.00 | 427.00 | 396.00 |
| 25th percentile | 639.54 | 620.00 | 661.00 | 669.00 | 633.77 |
| 75th percentile | 1031.49 | 1078.00 | 924.00 | 1014.00 | 1039.50 |
| 95th percentile | 1315.55 | 1404.00 | 1124.00 | 1327.00 | 1347.00 |
| Range | 274.90, 1643.55 | 197.00, 1481.00 | 248.00, 1720.00 | 143.00, 1336.00 | 143.00, 1720.00 |

References:

1. Yan et al., Immunity and Ageing 2010 v. 7:4; The effect of ageing on human lymphocyte subsets: comparison of males and females.
2. Wikby et al., Biogerontology 2008 vol 9: 299; The immune risk profile is associated with age and gender: findings from three Swedish population studies of individuals 20-100 years of age.
3. Horowitz eJIFCC 2008 vol. 19 (2) Reference intervals: practical aspects).
4. Horowitz et al., CLSI Vol 28 no. 30 Clinical and Laboratory Standards Institute's (CLSI) newly revised document Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition (C28-A3), published in November 2010 EP28-AC3

# PROTOCOL SIGNATURE PAGE

**Study Protocol Number:** E2609-G000-202
**Study Protocol Title:** A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability and Efficacy of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01)
**Investigational Product Name:** E2609
**IND Number:** 109308
**EudraCT Number:** 2014-002723-94

**SIGNATURES**
Authors:

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Eisai Inc.

Date

# INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability and Efficacy of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01) |
| **Investigational Product Name:** | E2609 |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

| Investigator | Signature | Date |
|---|---|---|

# REVISION HISTORY

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Grammatical, typographical, and formatting changes | | Throughout |
| Mandatory nature of CSF collection in study changed to voluntary. This change impacts the timing and details of the PK/PD interim analyses. It also impacts the nature of the CSF-related objectives, which will now be identified as exploratory. | To increase rate of subject consent into the study | • Synopsis –<br>○ Secondary Objectives<br>○ Exploratory Objectives<br>○ Study Design<br>○ Exclusion Criterion No. 12<br>○ Pharmacokinetic Assessments<br>○ Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments<br>○ Safety Assessments<br>○ Secondary Endpoints<br>○ Exploratory Endpoints<br>○ Analysis for the Secondary Endpoints<br>○ Analysis for the Exploratory Endpoints<br>• Section 5.3<br>• Section 8.2<br>• Section 8.3<br>• Section 9.1<br>• Section 9.1.1.2<br>• Section 9.2.6<br>• Section 9.3.2<br>• Section 9.4.6<br>• Section 9.5.1.3.3<br>• Section 9.5.1.4<br>• Section 9.5.1.5.12<br>• Section 9.7.1.1.2<br>• Section 9.7.1.1.3<br>• Section 9.7.1.6.2<br>• Section 9.7.1.6.3<br>• Section 12, Listing 2 |
| Extended the range of cognitive impairment in delayed recall that would be considered inclusionary for the study and removed the eligibility nature of the cognitive | Original delayed recall aspect of inclusion criterion #1 was considered to be too restrictive and was | • Synopsis –<br>○ Inclusion/ Exclusion Criteria<br>• Section 9.3.1<br>• Section 9.3.2 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| tests repeated at the Baseline Visit. | unnecessarily screening out subjects with MCI/prodromal AD. The eligibility nature of the cognitive tests repeated at the Baseline Visit has been removed in order to simplify the requirements of the pretreatment period for the study. | |
| Addition of historical amyloid PET scans for determination of eligibility for the study. Subjects with historical PET scans will not be part of the longitudinal PET analyses and therefore will not require a second PET scan at either Visit 18 or ED. | To provide the sites with greater operational flexibility and reduce subject burden. | • Synopsis –<br>  ○ Inclusion/ Exclusion Criteria<br>  ○ Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments<br>• Section 9.1.1<br>• Section 9.2.5.3<br>• Section 9.3.1<br>• Section 9.5.2, Table 6 and Table 7 |
| Added the need for safety laboratory tests to be repeated for subjects whose pre-treatment period is extended due to active infection. | To ensure that all baseline safety laboratory tests are repeated for subjects whose pretreatment period is extended. | • Synopsis –<br>  ○ Inclusion/ Exclusion Criteria<br>• Section 9.3.2<br>• Section 9.5.2, Table 6 |
| Clarified that exclusion criterion No. 22 (exclusion of subjects with CD4, CD8, or CD19 absolute counts below the LLN) applies to flow cytometry tests conducted at both the Screening and the Baseline Visits. Furthermore, LLNs that are adjusted for the subject population under study will be used. | It was not clear that Exclusion Criterion No. 22 applied to both the Screening and the Baseline Visits. The LLNs for CD4, CD8 and CD19 absolute counts require adjustment for the age of the patient population in this study. | • Synopsis –<br>  ○ Inclusion/ Exclusion Criteria<br>• Section 9.3.2 |
| Provided additional detail regarding scope of Exclusion Criterion No. 34 which excludes subjects with hypopigmentation conditions. | Added to provide clarity for the sites. | • Synopsis –<br>  ○ Exclusion Criteria<br>• Section 9.3.2 |
| Revised number of clinical sites | For feasibility purposes | • Synopsis – Sites |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| from 30 to 40 | | • Section 6<br>• Section 9.1<br>• Section 9.3 |
| Relaxed the requirement for the cognitive assessments at Screening Visit 1 to be conducted in a certain order and revised the recommended order in which the assessments could be conducted. | To provide the sites with greater operational flexibility. | • Section 9.1.1, Figure 2<br>• Section 9.5.1.3.1<br>• Section 9.5.2, Table 6 |
| Clarify the duration for which the Safety magnetic resonance imaging (MRI) scan, the amyloid PET scan and the lumbar puncture (LP) collected CSF conducted at Screening are considered valid. | To provide sites with greater operational flexibility, particularly for re-screening of screen fail subjects. | • Section 9.1.1 |
| Clarify that for subjects meeting criteria for weekly monitoring of lymphocyte subsets, these can be accommodated within the scheduled clinic visits during the early stages of the treatment period of the study. | To provide operational clarity to the sites. | • Synopsis –<br>○ Exclusion Criteria<br>• Section 9.3.2<br>• Section 9.3.3<br>• Section 9.5.1.5.3 |
| Added the requirement for complete blood counts (CBC) with differentials to be performed whenever repeat or unscheduled flow cytometry tests are performed. | Such that CBC data are available at all times when flow cytometry data is available. | • Section 9.3.3, Table 1<br>• Section 9.5.2,<br>○ Table 6<br>○ Table 7 |
| Added 30 day window to the duration of the pre-treatment period if required for medical or operational reasons. | To provide the sites with greater operational flexibility. | • Synopsis –<br>○ Study Design<br>○ Duration of Treatment<br>• Section 9.1, Figure 1<br>• Section 9.1.1<br>• Section 9.1.1.2<br>• Section 9.5.2, Table 6 |

**Revisions to Version 3.0**

**New version/date: Version 4.0, 05 Nov 2015**

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Clarified the timing of the start of the Randomization Phase | Clarification | • Section 9.1.1<br>• Section 9.1.2<br>• Section 9.5.2,<br>○ Table 6<br>○ Table 7 |
| Increased number of MCI/Prodromal or mild to moderate AD subjects screened for entry into the study | To reflect the higher screen failure rate than originally anticipated | • Synopsis –<br>○ Number of Subjects |
| Removal of CD127 cell surface markers | FoxP3 is the most accepted marker to measure T regulatory cells and additional assessment of CD127 is not required. | • Section 9.5.1.5.3, Table 4<br>• Section 9.5.2.1 |
| Made the clinical biochemistry, urinalysis, CBC, lymphocyte subsets, and immunoglobulin tests mandatory at Visit 20, regardless of clinical significance at Visit 19. | For more comprehensive safety data at the second follow-up visit. | • Section 9.5.2, Table 7 |
| Corrected reference to Exclusion Criterion No. 20 (and not to Exclusion #19) in footnote to Table 6 and Table 7 regarding timing of Visit 3 in relation to Visit 2. | Correction | • Section 9.5.2,<br>○ Table 6<br>○ Table 7 |
| Revised details regarding prohibited antiplatelet drugs | To distinguish between those subjects who consent to CSF sample collection and those who do not | • Appendix 2, Listing 2 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised inclusion to allow for enrollment of mild to moderate AD subjects in Stage A and expand the Stage B mild AD cohort to also include moderate AD subjects | To collect safety data in a wider range of AD patients. | • Title Page<br>• Synopsis –<br>  ○ Objectives<br>  ○ Study Design<br>  ○ Number of Subjects<br>  ○ Inclusion/Exclusion Criteria<br>  ○ Study Treatments<br>  ○ Efficacy Assessments<br>  ○ Study Endpoints<br>  ○ Efficacy Analyses<br>  ○ Interim Analyses<br>  ○ Adaptive Randomization<br>  ○ Sample Size<br>• Section 5.3<br>• Section 7<br>• Section 8 (and all subsections)<br>• Section 9.1, Section 9.1.1<br>• Figure 1<br>• Section 9.2.1, Section 9.2.2, Section 9.2.3<br>• Section 9.2.5.3 and Section 9.2.5.4<br>• Section 9.3, Section 9.3.1, Section 9.3.2<br>• Section 9.4.1, Section 9.4.3, Section 9.4.4<br>• Section 9.5.1.3.1<br>• Section 9.7.1.1.2, Section 9.7.1.1.3<br>• Section9.7.1.4<br>• Section 9.7.1.6, Section 9.7.1.6.2, Section 9.7.1.6.3<br>• Section 9.7.1.8.2<br>• Section 9.7.2.2<br>• Section 9.7.3<br>• Section 9.7.4 |
| Revised inclusion criteria for MMSE to ≥16 from ≥20 | The MMSE score is used as a cut-off for the most impaired subject that would be eligible for the study. Lowering the MMSE inclusion from ≥20 to ≥16 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD cohort. | • Synopsis – Inclusion/Exclusion Criteria<br>• Section 9.3.1 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised inclusion criteria for FAQ to ≤24 from ≤20 | As for the MMSE, the FAQ score is used as a cut-off for the most impaired subject that would be eligible for the study. Revising the FAQ inclusion from ≤20 to ≤24 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD cohort, and is consistent with an MMSE inclusion of ≥16. | • Synopsis – Inclusion/Exclusion Criteria<br>• Section 9.3.1 |
| Revised exclusion criteria such that small arachnoid cysts are not necessarily exclusionary | Arachnoid cysts are a common finding in otherwise healthy subjects. Small lesions (<1 cm in diameter) are generally not considered clinically significant and if discovered incidentally no long term follow up is routinely required. | • Synopsis – Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised exclusion criteria for Ig (IgG, IgA, or IgM) to specify that levels below the LLN at Screening or Baseline need not be exclusionary | For subjects with a Screening or Baseline IG level <LLN to be considered for continuation in the study, assessment of clinical significance of the finding will be required. A finding of "not clinically significant" must be agreed between the Investigator and Medical Monitor in order for the subject to continue in the study. | • Synopsis – Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised text to provide instructions for subject assent and associated consent by a legal representative for subjects who the Investigator considers not to have the capacity to consent themselves | With the expansion of the patient population to include moderately demented subjects it was necessary to provide directions regarding the consenting process for subjects considered to be lacking the capacity to consent themselves. | • Section 5.3 |
| Revised number of clinical sites to 30 from 25 | For feasibility purposes. | • Synopsis – Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Added allowance for Tier 1 and Tier 2 screening assessments to be performed on the same day | Added to provide operational clarity for the sites. | • Section 9.1.1.1<br>• Table 6 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Removed requirements for MRIs to include sequences for resting state functional MRI | This was an error and should not have been included in the original protocol. | • Table 6<br>• Table 7 |
| Revised text to clarify that on visits where CSF collection takes place, the CSF collection need not take place on the same day as the cognitive testing for that visit | Added to provide operational clarity for the sites. | • Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised text to clarify that the most important efficacy assessment to keep blinded from safety data is the CDR. | Added to provide operational clarity for the sites. | • Synopsis – Safety Assessments<br>• Section 9.4.6<br>• Section 9.5.1.5 |
| Revised text to allow PK blood sample and PD blood samples to be taken either shortly before or shortly after the LP on CSF days | Added to provide operational flexibility for the sites. | • Section 9.5.1.4.1<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised Sponsors Grading for Laboratory Values for the following analytes: lymphocytes, neutrophils, albumin, creatinine, phosphate, and potassium serum-high (hyperkalemia) | Corrections made to align with the values for grading used by the central clinical laboratory for this study. | • Appendix 1 |
| Revised details regarding prohibited antiplatelet drugs | Previous version incorrectly referenced a biomarker subgroup. All subjects in this study will need to provide CSF samples. | • Appendix 2; Listing 2 |
| Revised grammar, spelling, etc. | Compliance with current company style guide and for general consistency. | Throughout protocol |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revisions to grammar, spelling, etc. | Compliance with current company style guide and for general consistency | • Throughout protocol |
| Revisions made per new company protocol template | Alignment with current Eisai template | • Synopsis - Inclusion/Exclusion Criteria<br>• Section 9.1.2.3<br>• Section 9.3.1<br>• Section 9.3.2<br>• Section 9.5.1 (related subsections)<br>• Section 9.5.4<br>• Section 9.5.4.1<br>• Section 9.5.4.2<br>• Section 9.5.4.3 |
| Clarified classification of MCI due to AD | Clarification that MCI due to AD population will also be consistent with the research criteria for Prodromal AD in that impaired episodic memory is required and will be tested using a list learning task (the International Shopping List Task) | • Synopsis – Study Design<br>• Section 9.1 |
| Replaced “enroll” with “randomize,” pertaining to subject entry into study | Correction to terminology | • Synopsis – Study Design<br>• Section 9.1<br>• Section 9.3 |
| Added criterion excluding subjects with hepatic impairment and total bilirubin greater than 1.5×ULN or INR greater than 1.7 at Screening or Baseline. Subjects with Gilbert’s syndrome need not be excluded. | At request of FDA, exclude subjects who have hepatic impairment | • Synopsis – Inclusion/Exclusion Criteria<br>• Abbreviation List<br>• Section 9.3.2 |
| Added coagulation parameters for prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR) to screening and baseline procedures | Screen for hepatic impairment | • Synopsis – Inclusion/Exclusion Criteria<br>• Abbreviation list<br>• Section 9.3.2<br>• Table 4<br>• Table 6<br>• Table 8 |
| For subjects who discontinue study drug prematurely, conduct efficacy | To facilitate efficacy analyses, which are based on longitudinal | • Synopsis –Study Design<br>• Section 9.1.2.2<br>• Section 9.3.3 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| assessments postdose at same time points as subjects who continue in the study. Added FAQ to this set of efficacy assessments. | modeling for all subjects | • Section 9.5.4.1<br>• Section 9.5.5<br>• Table 7 |
| Delete diagram of E2609 structure | This display is not needed for the protocol. The Investigator's Brochure has this information. | • Section 9.4.2.1 |
| Additional blood samples to be taken at Visits 19 and 20 | Samples are to be put in storage to allow for assessment of immune status at end of study, as needed. | • Synopsis - Assessments<br>• Table 8 |
| Add subheadings to Section 9.7 describing the primary endpoint analysis, and text clarifying that no multiplicity adjustments will be done to account for the interim analyses | To distinguish clearly the primary analysis and the sensitivity analyses of the primary endpoint | • Synopsis - Efficacy Analyses<br>• Section 9.7.1.6.1 |
| Clarification of PK sampling upon Early Discontinuation | Additional operational details of the timing of the PK sampling at the ED visit provided | • Section 9.5.1.4.1<br>• Table 7 |
| Clarification of ApoE testing | Clarification that the ApoE genetic testing will be for homozygous or heterozygous E4, versus non-E4 | • Section 9.5.1.4.2 |
| Revision to PK/PD interim analysis text | Confirm that interim PK/PD analysis will be conducted by an independent group | • Section 9.4.6 |
| Addition of text regarding safety signals with E2609 | To provide information on safety-driven dose adjustments | • Synopsis – Study Design<br>• Section 9.1 |
| Addition of PBMC collection/assessment at Baseline, during treatment, and posttreatment | Recent animal studies have shown an effect of E2609 on this model so they will be added to the 202 clinical study as an additional exploratory assessment. | • Synopsis – Safety Assessments<br>• Section 9.2.6<br>• Section 9.5.1.5<br>• Table 4<br>• Table 6<br>• Table 7<br>• Table 8 |
| Stipulate that exploratory biomarker analyses may be conducted using blood or CSF samples that may have been drawn for other purposes | To allow more flexibility for possible exploratory biomarker studies associated with study drug or disease, including miRNA and DNA | • Synopsis - Assessments,<br>• Abbreviation list<br>• Section 9.5.1.4.2<br>• Section 9.5.1.5.12<br>• Table 6<br>• Table 7 |
| Prohibit concomitant medications that are strong CYP3A4, inhibitors, but clarify that no restrictions are | At request of FDA, in light of finding that inhibition of CYP3A4 by a reference agent increases | • Synopsis - Concomitant Drug/Therapy<br>• Section 7.1 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| needed for other CYP3A4 inhibitors, CYP3A4 inducers, or CES2 inhibitors | plasma levels of E2609 | • Section 9.4.7<br>• Appendix 2(Listing 6) |
| Addition of tests for viral characterization at Baseline | To confirm by serology information of subjects prior exposure to common viruses pre-dosing with study drug | • Section 9.5.1.2.2<br>• Table 4<br>• Table 6<br>• Table 8 |
| Use of a centralized dermatologist assessment via photography | A centralized approach, using standardized photography, to FDA-required serial dermatological assessments will be employed for consistency of assessments between sites and for consistency of longitudinal assessments of individual subjects. | • Synopsis – Safety Assessments<br>• Section 9.2.6<br>• Section 9.5.1.5<br>• Section 9.5.1.5.8<br>• Table 6<br>• Table 7 |
| Removal of testing for benzodiazepines or opioids as part exclusion criteria #35 | To differentiate appropriate medicinal use from recreational drug use or abuse | • Synopsis – Exclusion Criteria<br>• Section 9.3.2 |
| Addition of analysis of other covariates such as adjusted hippocampal volume will be studied | Hippocampal volume has been shown to correlate with rate of cognitive decline and as such is a key covariate to be used in the analyses. | • Synopsis – Analysis of Primary Endpoint<br>• Section 9.7.1.6.1 |
| Addition of clarifications to ophthalmic examination | To provide more detail around the requirements for the ophthalmic exam | • Synopsis – Safety Assessments<br>• Section 9.5.1.5.13<br>• Table 6<br>• Table 7 |
| Addition of details regarding specific method of CSF collection (ie, gravity drip) | Use of materials required for suction method when collecting CSF can affect the PD data and so it is important to make it clear that only the gravity drip method can be used for collecting CSF in this study for protecting the quality and the consistency of the CSF PD data. | • Section 9.5.1.3.3<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Addition of specific testing for B12 levels at Screening | Abnormally low serum vitamin B12 levels are exclusionary for the study (excl criterion 8) but a blood draw for Vit B12 was inadvertently missed out of Table 6 in protocol version 1. | • Synopsis – Exclusion Criteria<br>• Section 9.3.2<br>• Section 9.5.1.2.3<br>• Figure 2<br>• Table 6 |
| Addition of details regard AEs that might be signals of possible drug abuse potential | Changed terminology re: collection of additional information for AEs that might be signals of possible | • Synopsis – Safety Assessments<br>• Section 9.2.6<br>• Section 9.5.1.5.1 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | abuse potential. No longer use the word "narrative" in order to avoid potential confusion with standard clinical trial narratives eg, for serious adverse events, adverse events leading to withdrawal, etc. | • Appendix 4 |
| Addition of clarification regarding position for taking vital signs (ie, supine) | The American Heart Association guidelines only mention supine, standing, and sitting as positions for taking HR and BP measurements. Therefore, have changed required position from semi-supine to sitting. | • Section 9.5.1.5.4<br>• Table 6<br>• Table 7 |
| Stipulated that study drugs are to be taken with food | For consistency of treatment conditions | • Section 9.5.1.4.1 |
| Change to list of Study Specific AEs which should be considered SAEs | Eisai's standard procedures have changed such that non-serious study specific adverse events of interest are no longer reported to Eisai Product Safety; instead, any additional information required for such non-serious adverse events will be obtained through other methods. In addition, certain events (new onset seizures, ocular herpes) are now to be classified as serious as important medical events, regardless of whether they meet standard ICH serious criteria. | • Section 9.5.1.5.1<br>• Section 9.5.1.5.2 |
| Increased blood volume for PK | To match collection tubes and ensure sufficient sample for planned assays | • Table 8 |
| Corrected error in definition of PK analysis set | For accuracy | • Synopsis – Study Endpoints<br>• Section 9.7.1.2 |
| Addition of details regarding discontinuation of study drug | To clearly and consistently differentiate "discontinuation from study drug" from "withdrawal from study" | • Synopsis<br>• Section 7<br>• Section 9.1.2.1<br>• Section 9.2.6<br>• Section 9.3.3<br>• Table 1<br>• Table 2<br>• Section 9.4.1<br>• Section 9.4.4<br>• Section 9.5.1.5.1<br>• Section 9.5.1.5.3<br>• Section 9.5.5 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Re-ordered prohibited medication lists | For consistency, all lists re-ordered in alphabetical order of generic drug name, and footnotes revised for overall consistency | • Appendix 2 |
| Moved nefazodone from Listing 9 to Listing 6 | Nefazodone is a strong CYP3A4 inhibitor and is therefore prohibited. | • Appendix 2 |

# 1 TITLE PAGE


## Clinical Study Protocol

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability, and Efficacy of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01) |
| **Sponsor:** | Eisai Inc.<br>155 Tice Boulevard<br>Woodcliff Lake,<br>New Jersey 07677<br>United States<br><br>Eisai Ltd.<br>European Knowledge Centre<br>Mosquito Way<br>Hatfield, Hertfordshire<br>AL10 9SN<br>United Kingdom<br><br>Eisai Co., Ltd.<br>4-6-10 Koishikawa<br>Bunkyo-Ku,<br>Tokyo 112 8088<br>Japan |
| **Investigational Product Name:** | E2609 |
| **Indication:** | Alzheimer's disease |
| **Phase:** | 2 |
| **Approval Date:** | V1.0 15 Jul 2014 (original protocol)<br>V2.0 21 Oct 2014 (revised original protocol)<br>V3.0 28 May 2015 (Amendment 01)<br>V4.0 05 Nov 2015 (Amendment 02) |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |
| **GCP Statement:** | This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities. |
| **Confidentiality Statement:** | This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study. |

# 2 CLINICAL PROTOCOL SYNOPSIS

**Compound No.:**

E2609

**Name of Active Ingredient:**

*N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

**Study Protocol Title**

A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability, and Efficacy of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01)

**Investigators**

Stage A: Investigators in United States only

Stage B: Multinational investigators

**Sites**

Stage A: Approximately 40 sites, United States only (revised per Amendments 01 and 02)

Stage B: Approximately 125 sites, globally

**Study Period and Phase of Development**

Stage A: Approximately 32 months and will continue and overlap with Stage B

Stage B: Approximately 42 months from initiation of Stage B (revised per Amendment 01)

Phase 2

**Objectives**

**Primary Objectives**

1. To evaluate the efficacy of daily dosing with 3 doses of E2609 compared with placebo by establishing the lowest effective dose that achieves 90% of the greatest treatment effect ($ED_{90}$) for E2609 on the derived Alzheimer's Disease Composite Score (ADCOMS) at 18 months of treatment in subjects with Mild Cognitive Impairment due to Alzheimer's Disease/ Prodromal Alzheimer's Disease (referred to as MCI/Prodromal throughout the protocol)
2. To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with Mild to Moderate Dementia due to Alzheimer's Disease (referred to as mild to moderate AD throughout the protocol) (revised per Amendment 01)

**Secondary Objectives** (revised per Amendment 02)

1. To evaluate the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects, as measured by volumetric magnetic resonance imaging (vMRI)
2. To evaluate the efficacy of E2609 compared with placebo on the derived ADCOMS at 18 months in mild to moderate AD subjects (revised per Amendment 01)

**Exploratory Objectives**

(revised per Amendments 01 and 02)

1. To explore the effect of E2609 compared with placebo on the derived ADCOMS following 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
2. To explore the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in mild to moderate AD subjects, as measured by vMRI
3. To explore the effects of E2609 compared with placebo on Aβ(1-x) and Aβ (1-42) in CSF after 4 weeks and 18 months of treatment in MCI/Prodromal subjects and in mild to moderate AD subjects (revised per Amendment 02)
4. To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during post-treatment follow-up, in MCI/Prodromal and mild to moderate AD subjects, by assessment of:
   a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
   b. The Clinical Dementia Rating (CDR) scale
   c. The Mini-Mental State Examination (MMSE)
   d. The CogState Brief Battery (CBB)
   e. The Functional Assessment Questionnaire (FAQ; also known as the Functional Activities Questionnaire)
   f. The International Shopping List Task (ISLT)
5. To explore the effects of E2609 compared with placebo on various biomarkers in MCI/Prodromal and mild to moderate AD subjects. Biomarkers to be explored include:
   a. CSF biomarkers of neurodegeneration (eg, tau, phosphorylated-tau [p-tau]) after 18 months of treatment
   b. Plasma and CSF amyloid, and CSF β-amyloid converting enzyme 1 (BACE1) measurements during 18 months of treatment and during posttreatment follow-up
   c. vMRI measurements including left and right hippocampal volume, whole brain volume and total ventricular volume at 6, 12, and 18 months of treatment and during post-treatment follow-up
   d. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)
6. To characterize the population pharmacokinetics (PK) of E2609 in MCI/Prodromal and mild to moderate AD subjects, and to examine the effect of intrinsic and extrinsic factors (including N-acetyltransferase 2 [*NAT2*] phenotype) on the PK
7. To explore the relationship between the treatment effects of E2609 on the ADCOMS and its effects on CSF amyloid, CSF BACE1, CSF tau, and vMRI in MCI/Prodromal and mild to moderate AD subjects

**Study Design**

This will be a multicenter placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild to moderate AD. A common set of inclusion criteria, consistent with the National Institute on Aging – Alzheimer's Association (NIA-AA) clinical research criteria for Mild Cognitive Impairment (MCI) due to Alzheimer's Disease (AD) or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with the criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal

subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study will be conducted in 2 stages, Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 (after the first 60 randomized subjects have completed 12 weeks of treatment or have discontinued study drug early) before expanding enrollment to include a larger number of subjects in Stage B. (revised per Amendment 01) All MCI/Prodromal subjects will be included in the primary efficacy evaluation irrespective of whether they were recruited during Stage A or Stage B. Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B. All mild to moderate AD subjects will be included in the efficacy evaluations for that cohort. (revised per Amendment 01)

Both Stage A and Stage B will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days, plus an additional window of up to 30 days if required [revised per Amendment 02]) includes a Screening Visit (Visit 1) and a Baseline Visit (Visit 2). All screening assessments (within 4 distinct tiers) must be completed, and eligibility to continue in the study confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

**Stage A**

Stage A will be limited to approximately 40 sites in the United States. (revised per Amendments 01 and 02) Stage A will randomize 60 eligible subjects at Visit 3, 1:1:1:1 to 4 treatment groups within each of the 2 clinical populations. (revised per Amendment 01) In addition to the placebo group, 3 E2609 doses will be used to reduce CSF amyloid β levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/pharmacodynamic (PD) modeling has shown that these doses should achieve these targets when administered once daily (QD) with food, and these doses will be evaluated based on the 4-week assessment of CSF Aβ(1-x) from subjects who provide voluntary consent for CSF measurement. (revised per Amendment 02)

During Stage A, safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the first subject is randomized during Stage A, an independent data safety monitoring board (DSMB; including at least 1 immunologist) will review all safety data in an unblinded manner. The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. Unless the DSMB recommends otherwise, randomization of subjects into Stage A will continue until 60 subjects have been randomized and dosed. (revised per Amendment 01)

Interim analyses of the E2609 PK and PD profiles will be performed on subjects who consent to provide CSF samples at Baseline and after 4 weeks of study drug. These data will be used to evaluate the CSF PD effects of E2609 doses, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels. (revised per Amendments 01 and 02) The mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment for each dose of E2609 and its 90% confidence interval will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data from Stage A and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline after 4 weeks of dosing. (revised per Amendment 02)

Once 60 subjects in Stage A have completed at least 12 weeks of treatment (or discontinued study drug early) an interim safety analysis will be conducted by Eisai and the DSMB. (revised per

Amendment 01) Subjects in Stage A will continue study drug while the DSMB reviews all the available safety data, but randomization of additional subjects will not take place (ie, recruitment into Stage B will not commence) until the safety analysis is completed by the DSMB.

If there are safety signals with one of the E2609 dose groups that would require dose adjustment, changes to dose will be reflected in an amendment to the protocol. Information on how these subjects will be handled in the primary analysis will be described in the Statistical Analysis Plan.

**Stage B**

Stage B will start after the DSMB safety review of Stage A has shown acceptable safety and tolerability of E2609 and after the doses of E2609 to be used in Stage B are evaluated. (revised per Amendment 02) Stage B will enroll, randomize, and dose additional eligible subjects up to a maximum of 500 MCI/Prodromal and up to a maximum of 200 mild to moderate AD. The final total number of MCI/Prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. (revised per Amendment 01) Safety data from Stage B will continue to be reviewed by the DSMB (approximately every 3 months) until recruitment to the study is completed; following this the DSMB will meet approximately every 6 months.

In Stage B, both cohorts will include separate placebo groups. The MCI/Prodromal cohort will include 3 doses of E2609 (5, 15, and 50 mg QD) whereas the Mild to Moderate AD cohort will only include 2 doses of E2609 (15 and 50 mg QD). (revised per Amendment 01)

Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B. Randomization of MCI/Prodromal subjects into Stage B will commence according to a fixed schedule (1:1:1:1; placebo:5 mg E2609:15 mg E2609:50 mg E2609) until a total of 100 MCI/Prodromal subjects (including those from Stage A) have been randomized. (revised per Amendment 01) The remaining subjects in the MCI/Prodromal cohort in Stage B will then be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. The mild to moderate AD subjects will be randomized according to a fixed schedule (1:1:1 placebo; 15 mg E2609; 50 mg E2609) throughout Stage B. (revised per Amendment 01)

**Early Discontinuation**

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug. Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie, at Visits 11, 14, 15, 16, 17, and 18) if these visits have not already been performed. At these visits, only the clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB and ISLT) will be conducted. Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

**Follow-Up**

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug (Visit 19) and a second 12 weeks after the last dose of study drug (Visit 20). If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the posttreatment Follow-Up period.

**Number of Subjects**

- Stage A: Approximately 400 MCI/Prodromal or mild to moderate AD subjects will be screened to provide 60 randomized subjects (target of 15 subjects per treatment arm). There will be no limit to the number of subjects randomized from either clinical cohort. (revised per Amendments 01 and 02)
- Stage B: Up to approximately 2100 MCI/Prodromal subjects will be screened to provide up to 500 randomized subjects. The final number of MCI/Prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. In addition, up to approximately 835 subjects with mild to moderate AD will be screened to provide up to 200 randomized mild to moderate AD subjects. The final number of mild to moderate AD subjects randomized in Stage B will depend upon the number of mild to moderate AD subjects previously randomized during Stage A. (revised per Amendment 01)

**Inclusion Criteria**

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD or AD dementia and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at Screening Visit 1:**
(revised per Amendment 02)

   a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation
   b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT. Alternatively, cognitive impairment of at least 0.5 SD from age-adjusted norms in delayed recall on the ISLT plus impairment of at least 1 SD from age-adjusted norms in at least 1 other computerized learning and memory test (ISLT immediate recall, or 1 of the learning and memory components of the CBB). (revised per Amendment 02)
   c. FAQ $\leq$24 (revised per Amendment 01)
   d. MMSE $\geq$16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading; an historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group (revised per Amendment 02)
3. Male or female, age 50 to 85 years, inclusive at time of consent
4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.
5. If receiving acetylcholinesterase inhibitors (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.
6. Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization.

**Exclusion Criteria**

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or magnetic resonance imaging (MRI)

2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and < 1cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could, in the opinion of the investigator, confound the MCI/Prodromal or mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendments 01 and 02)
7. A score of ≥8 on the 15-item Geriatric Depression Scale at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the lower limit of normal (LLN) for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
12. Any contraindications to lumbar puncture for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity). Only applicable to subjects consenting to CSF sample collection (revised per Amendment 02)
13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles

18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization
20. Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below population-adjusted LLN at Screening or Baseline and confirmed by a repeat test conducted 1 week after the initial test. The population-adjusted LLN for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are 396, 157, and 74 cells/μL respectively. (revised per Amendment 02)
23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the Investigator and the Medical Monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of clinical immunodeficiency. The discussion with the Medical Monitor should include a detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)
24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate electrocardiograms (ECGs). A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute at Screening or Baseline
29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy;

these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.

33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo). Diagnosis of an underlying disease causing hypopigmentation is not necessary for exclusion if the clinical presentation is consistent with such a condition. Hypopigmentation associated with scarring need not be exclusionary. (revised per Amendment 02)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period and for 28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.

- Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
  (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

44. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or not practicing highly effective contraception throughout the study period or for 28 days after study drug discontinuation). No sperm donation is allowed during the study period or for 28 days after study drug discontinuation.

**Study Treatments**

E2609 tablets of 5-mg, 10-mg and 25-mg dose strengths will be supplied. Placebo tablets to match E2609 will be of identical appearance. Each subject will receive 2 tablets, which when combined will make up the required doses of E2609 (see below) or placebo, to be administered orally QD with food.

- Stage A: 3 doses (5, 15, and 50 mg) of E2609 or placebo (revised per Amendment 01)
- Stage B, MCI/Prodromal Cohort: 3 doses (5, 15, and 50 mg) of E2609 or placebo (revised per Amendment 01)
- Stage B, Mild to Moderate AD Cohort: 2 doses (15 and 50 mg) of E2609 or placebo. (revised per Amendment 01)

**Duration of Treatment**

The maximum duration of a subject's participation in the study will be approximately 2 years, comprising:

- Screening and Baseline Periods (Prerandomization Phase): up to 60 days, plus an additional window of up to 30 days if required (revised per Amendment 02)

  (In subjects who have an active infection within 4 weeks of the planned randomization date, the duration of the pre-randomization phase can be extended by up to 4 weeks to allow additional time for resolution of the infection.)
- Treatment Period (Randomization Phase): up to 78 weeks
- Follow-Up Period (Randomization Phase): 12 weeks (post last dose)

**Concomitant Drug/Therapy**

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit (see Appendix 2 for a detailed listing of these agents):

- Anticoagulants (eg, warfarin, digabatrin) are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization
- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization

Subjects taking AChEIs or memantine must meet the following criteria in order to be included in the primary analyses:

- On a stable dose for 12 weeks before the baseline cognitive assessments at Visit 2
- Remain on a stable dose while on study

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for the primary analyses.

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if, in the opinion of the investigator, this will not interfere with study procedures or subject safety, and are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks.

**Assessments**

**Efficacy Assessments**

Derived ADCOMS: The derived ADCOMS represents a new approach to the analysis of selected items (12 total) from 3 fully validated and well established clinical tools, the ADAS-cog (4 items), the MMSE (2 items), and the CDR (all 6 items). The 3 scales should be administered in full in the

morning, or, if not possible, consistently at the same time of day.

Alzheimer's Disease Assessment Scale - cognitive subscale: The 14-item version will be used since it is considered more relevant for subjects with MCI/Prodromal AD or mild AD.

Mini Mental State Examination: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing.

Clinical Dementia Rating: Assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

CogState Brief Battery: A computer-based battery comprising 4 cognitive tests:

1. Detection – a simple reaction time test. Speed of response is the measure.
2. Identification – a simple choice reaction time test. Speed of response is the measure.
3. One Card Back – a simple working memory test. Accuracy of response is the measure.
4. One Card Learning – a visual learning and memory test. Accuracy of response is the measure.

International Shopping List Task: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall.

Functional Assessment Questionnaire: The FAQ has 10 items concerned with performing daily tasks necessary for independent living. Either a caregiver or informant or the subject provides performance ratings on 10 complex activities of daily living performed within the preceding 4 weeks.

Volumetric Magnetic Resonance Imaging: vMRI will be used to evaluate disease modification, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs.

**Pharmacokinetic Assessments**

Blood samples will be collected for the determination of the concentrations of E2609. For subjects who consent to CSF sample collection, CSF samples will be collected for the determination of E2609 concentrations. (revised per Amendment 02) Analyses of metabolite concentrations may be performed depending on emerging data from other studies with E2609.

**Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments**

Brain atrophy will be measured by vMRI: see Efficacy Assessments (above).

The soluble biomarkers Aβ(1-x), Aβ(1-42), total tau (t-tau), and p-tau will be measured in subjects who consent to CSF sample collection (revised per Amendment 02). BACE1 levels and activity in CSF will also be measured in subjects who consent to CSF sample collection (revised per Amendment 02). Other exploratory biomarkers (eg, miRNA) may also be evaluated in plasma and/or CSF.

Amyloid PET imaging will be used to confirm that all subjects eligible for progression to the Baseline Period have amyloid deposition in the brain. An historical amyloid positive PET scan may be used, if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02) Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses) and will only be conducted through to the time at which acceptable 18-month PET scans have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used. (revised per Amendment 02)

Apolipoprotein E (*ApoE*) and *NAT2* genotyping/phenotyping will be conducted. *ApoE4* homozygous or heterozygous status versus non-carriers and *NAT2* status will be used in the statistical analysis to determine the effects on treatment response and safety. Remaining genomic DNA may also be stored for up to 15 years to be used to examine the role of DNA sequence variability on the absorption, distribution, metabolism, and elimination of E2609, development of AEs, as well as the underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single-nucleotide polymorphisms with PK, safety, or PD data.

**Safety Assessments**

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR. (revised per Amendment 01) Routine safety assessments will include the monitoring and recording all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

Complete blood counts and lymphocyte subset absolute counts and percentages will be measured (by a centralized laboratory) every week for the first month, every 2 weeks for the next 2 months (Months 2 and 3) and monthly for the next 3 months (Months 4, 5, and 6). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits. Serum IgG, IgA, and IgM will be monitored monthly for the first 3 months, at 6, 12, and 18 months, and at both Follow-Up Visits.

Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and posttreatment for exploratory immunomodulatory and immune-based analyses.

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at baseline and at 3-month intervals during the Treatment Period. These assessments will specifically include evaluation of any areas of depigmentation or rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregivers/ informants will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so such AEs can be reviewed promptly.

Baseline and on-study blood and DNA samples will be taken and stored for all subjects, and CSF samples will be taken and stored for all subjects who consent to CSF sample collection (revised per Amendment 02). These samples may be tested for exploratory biomarkers associated with study drug or disease, or in the event that a subject develops AEs that warrant further investigation (eg, to test if a subject with a treatment-emergent infection was exposed to any suspected infective agents before treatment with study drug).

Safety brain MRI assessments will be performed at Screening, at 6, 12, and 18 months during the Treatment Period and at the final Follow-Up Visit. Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Full neurological examinations will be performed at Baseline, at 6, 12, and 18 months, and at both Follow-Up Visits, by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations. The neurological examinations will include muscle strength

testing and assessment of cranial nerves including olfaction as well as other parts of the CNS.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments will include the ADAS-$cog_{14}$, MMSE, and CBB.

An assessment of suicidality using the C-SSRS will be performed at Screening and Baseline and at regular intervals throughout the Treatment and Follow-Up Periods.

An ophthalmic examination (including retinal examination) will be conducted at Baseline. An additional examination will be conducted if the subject experiences visual disturbances during the course of the study.

A number of safety-related criteria for discontinuation of study drug are specified for the study.

**Bioanalytical Methods**

Plasma and CSF concentrations of E2609 will be measured by a validated liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) in both CSF and plasma will be measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and post-screening analysis of CSF Aβ(1-42), tau, and p-tau will be performed using ELISAs.

BACE1 levels and activity may be measured using a customized assay. Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

**Statistical Methods**

All statistical tests will be based on the 5% (2-sided) level of significance, except for the Bayesian methods on the primary endpoint.

**Study Endpoints**

**Primary Endpoint**

- Change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects

**Secondary Endpoints**

Change from baseline in: (revised per Amendment 02)

- Total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- The derived ADCOMS at 18 months of treatment in mild to moderate AD subjects (revised per Amendment 01)

**Exploratory Endpoints**

(revised per Amendments 01 and 02)

Change from baseline in:

- The derived ADCOMS at 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
- Total hippocampal volume at 12 and 18 months of treatment in mild to moderate AD subjects as measured by vMRI

- CSF Aβ(1-x) and Aβ(1-42) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects and in mild to moderate AD subjects (revised per Amendment 02)
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ in MCI/Prodromal and mild to moderate AD subjects
- CSF biomarkers of neurodegeneration (eg, tau and p-tau) at 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects
- Plasma and CSF amyloid, and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild to moderate AD subjects
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and, 18 months in MCI/Prodromal and mild to moderate AD subjects as measured by vMRI
- Brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- The population PK parameters of E2609 including the effect of intrinsic and extrinsic factors (including *NAT2* phenotype) in MCI/Prodromal and mild to moderate AD subjects

**Analysis Sets**

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set is the subset of subjects in the FAS who sufficiently comply with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

**Efficacy Analyses**

***The MCI/Prodromal cohort:*** This study in the MCI/Prodromal cohort is based on Bayesian adaptive design. Frequent interim analyses will be performed to assess the probability of early success and futility and to make early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis. Key definitions relevant to the Bayesian aspects of the adaptive design are given below.

**Study Definitions**

- **Maximum Effective Dose ($d_{Max}$):** The dose that achieves the greatest treatment effect.
- **$ED_{90}$:** The lowest dose that achieves at least 90% of the $d_{Max}$ treatment effect in the derived ADCOMS.
- **Early Success:** The study in the MCI/Prodromal cohort will meet early success criteria if the probability that the $ED_{90}$ at 18 months of treatment achieves 25% improvement over placebo is at least 80%. Early success is achieved before all MCI/Prodromal subjects complete 18 months of treatment and can only be determined after at least 200 MCI/Prodromal subjects have been randomized. If early success is declared before full randomization, the

randomization of new MCI/Prodromal subjects will stop but subjects already randomized into the study will receive the full 18 months of treatment (following confirmation from the Sponsor's Senior Management).

- **Futility:** The study in the MCI/Prodromal cohort will meet statistical futility criteria if the probability that the $ED_{90}$ is better than placebo by the clinically significant difference of 25% is less than 5% at 18 months of treatment. The statistical futility boundary is binding; if the statistical futility boundary is crossed the study will be considered to have failed.
- **Study Success:** The study in the MCI/Prodromal cohort will be considered a success if an $ED_{90}$ at 18 months treatment has at least an 80% probability of achieving 25% improvement over placebo at either an interim analysis or at the final analysis.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)***:*** All mild to moderate AD subjects will be included in the efficacy evaluations of the Mild to Moderate AD cohort. The analysis of the Mild to Moderate AD cohort is based on the group sequential design. Interim analyses in the Mild to Moderate AD cohort will only be performed after the MCI/Prodromal cohort crosses the early success boundary. The early efficacy signal based on the change from baseline of ADCOMS at 18 months is defined as crossing the interim-analysis boundaries for overwhelming efficacy in the mild to moderate AD population. The O'Brien-Fleming (OF) boundaries based on Lan-DeMets alpha spending function will be used to assess overwhelming efficacy. The corresponding OF boundaries based on *P* values will be 0.076, 0.0221, and 0.0423 for the first, second, and final analyses, respectively, according to 2 planned interim analyses at the 60% and 80% information fraction. (revised per Amendment 01)

**Analysis for the primary endpoint**

***Primary analysis of primary endpoint***

The primary analysis will be based on MCI/Prodromal subjects from the FAS with the prespecified censoring rule applied. The primary endpoint is the change from baseline to 18 months in the derived ADCOMS. The dose-response of the primary endpoint is modelled with a first-order normal dynamic linear model, where Normal and Inverse-Gamma priors are used. The primary efficacy analysis will calculate the Bayesian posterior probability that the dose identified is the most likely $ED_{90}$ dose that achieves 25% improvement over the placebo arm. At each interim analysis and the final analysis, 2 Bayesian probabilities will be summarized for each active dose: the probability it is the $ED_{90}$ dose and the probability of achieving 25% improvement over the placebo arm.

For the clinical efficacy data (ie, derived ADCOMS, MMSE, ADAS-cog, CDR, CBB, ISLT, and FAQ), subjects will be censored at the time of initiation of treatment with AChEIs or memantine, if they were not on these medications at the time of Baseline cognitive assessment (Visit 2), and will be censored at the time of dose adjustment of AChEIs or memantine if they were already on stable treatment with these medications at the time of Baseline cognitive assessment (Visit 2). The value of the primary endpoint for censored subjects will be imputed using data up to the censoring time and Bayesian longitudinal modeling.

***Sensitivity analyses of primary endpoint***

After unblinding, the primary endpoint will be analyzed using the Bayesian methods described above as well as conventional statistical methods. The following additional Bayesian analyses will be conducted as sensitivity analyses:

- The primary endpoint will be analyzed regardless of initiation of treatment, or dose adjustment, with AChEIs or memantine using the same Bayesian analysis method as primary analysis. This is an intent-to-treat analysis without any censoring.

- In case of early success, the primary analysis as well as the above sensitivity analyses will be repeated after all subjects have completed 18 months of treatment or have been lost to follow-up.

Statistical methods for the final conventional analyses will use a mixed-effects model with repeated measures (MMRM) on the change from baseline in the derived ADCOMS at 18 months. The model will include treatment groups, randomization stratification variables (the presence or absence of ongoing treatment with AChEIs or memantine or both, and *ApoE4* status), and baseline ADCOMS as covariates. Other covariates such as adjusted hippocampal volume will be studied. These analyses will be performed as sensitivity analyses on the FAS as well as the per protocol set, and as such, no multiplicity adjustments will be made to account for the interim analyses. In case of early success, the conventional analyses will also be performed using the data collected before the interim analysis.

**Analysis for the secondary endpoints**

***The MCI/Prodromal Cohort***

An MMRM will be used to analyze the following secondary endpoint: (revised per Amendment 02)

- Change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI

Comparisons between each treatment group and placebo will be performed.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

An MMRM will be used to analyze the change from baseline of derived ADCOMS at 18 months in mild to moderate AD. If there is no treatment group-by-population interaction in the overall study, the MMRM analysis will include all subjects (MCI/Prodromal or mild to moderate AD) in the overall study. Otherwise, the MMRM analysis will only include subjects in the Mild to Moderate AD cohort. The comparison between placebo and active doses will be performed within mild to moderate AD subjects regardless of subjects included in the MMRM analysis. Dunnett's method will be used to control for multiplicity due to multiple comparisons.

**Analysis for exploratory endpoints**

(revised per Amendments 01 and 02)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in the derived ADCOMS at 12 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in total hippocampal atrophy at 12 and 18 months in mild to moderate AD subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) after 4 weeks and 18 months in MCI/Prodromal and mild to moderate AD subjects. Data from early discontinuations will also be included. (revised per Amendment 02)
- Change from baseline in the clinical assessments: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in plasma and CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and 18 months as measured by vMRI in MCI/Prodromal and mild to

moderate AD subjects

A linear mixed-model will be used to analyze the following exploratory endpoints:

- Change from baseline in brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in CSF biomarkers of neurodegeneration (eg, tau, p-tau) at 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects

Data from early discontinuations will also be used as appropriate. Comparisons between each treatment group and placebo will be performed.

A linear mixed-model with repeated measures will be used to determine the relationship between the following endpoints:

- Change from baseline in the derived ADCOMS score and the change from baseline in biomarkers in CSF at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in the derived ADCOMS score and change from baseline in imaging biomarkers (hippocampal, whole brain, and total ventricular volumes) at 12 and 18 months in MCI/Prodromal and mild to moderate AD subjects

*ApoE* status for heterozygous and homozygous E4 carriers will be included in the model to assess the effect of *ApoE* status in this relationship.

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). CSF Aβ(1-x), Aβ(1-42), t-tau, p-tau, and BACE1 will be assessed and data will be presented graphically. Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status. Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels and exposure to E2609 in plasma and CSF will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. Additionally, the relationship between CSF exposure to E2609 and the derived ADCOMS at 18 months, and the relationship between CSF exposure to E2609 and the change from baseline for 18 months in the ADAS-cog, the CDR, and the

MMSE will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling.

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. Further information is in the "Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments" section. Details of pharmacogenomic testing may be provided and reported separately.

**Safety Analyses**

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, and vital sign measurements will be summarized

by treatment group using descriptive statistics.

Lymphocyte Subsets

Lymphocyte subsets (ie, CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages]) and regulatory T cells will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose. Serum IgG, IgM, IgA will be measured and summarized in the same manner as other laboratory parameters.

**Interim Analyses**

An interim safety analysis will be conducted when the first 60 subjects have completed 12 weeks of treatment (or discontinue study drug early) in Stage A. (revised per Amendment 01)

***The MCI/Prodromal Cohort***

Oversight of the Bayesian interim analyses and response adaptive randomization will be conducted by an independent committee that has expertise with Bayesian adaptive design in clinical studies. An unblinded external independent analysis group will provide the interim analysis outcomes to the committee at each interim analysis. The committee will ensure the integrity of the interim analysis and response adaptive randomization process through review of efficacy data. In addition, the committee will act in an independent advisory capacity to monitor the Bayesian interim analysis outcomes according to the early success and futility boundaries prespecified in the protocol. The committee will not be charged with any subject safety issues; this will remain the responsibility of the DSMB. The DSMB will continue to monitor the safety aspects of the study throughout Stage A and Stage B. The study may be stopped for safety at any time.

The first Bayesian adaptive interim analysis will be conducted when 100 MCI/Prodromal subjects have been randomized into the study (ie, including MCI/Prodromal subjects from both Stage A and Stage B). (revised per Amendment 01) Further interim efficacy analyses will be conducted after each additional 50 MCI/Prodromal subjects have been randomized, up to a maximum of 500 MCI/Prodromal subjects (ie, at 100, 150, 200, 250, 300, 350, 400, 450, 500 subjects randomized). If the study reaches full randomization, additional interim analyses will be conducted every 3 months until all subjects complete 18 months of treatment. The study will be monitored for futility at each interim analysis. Starting at the 200 subjects' interim analysis, the study will be monitored for success at each interim analysis. Each interim analysis will be conducted on data for the derived ADCOMS.

If the predefined early success criteria are met during the recruitment period, further recruitment and enrollment of MCI/Prodromal subjects into the study will stop (following confirmation from the Sponsor's Senior Management) and all currently randomized subjects will complete the full 18 months of treatment. No further interim analyses will be conducted after achieving early success.

If the predefined threshold for futility is reached, no additional subjects will be randomized into the study and the treatment of subjects already randomized into the study will stop and the study will be declared as "failed". All subjects will be monitored for safety for 3 months following their last dose.

If neither early success nor futility is reached and the study reaches full randomization, all subjects will complete 18 months of treatment. Interim efficacy analyses will be conducted every 3 months after full randomization is reached to assess futility and early success until all subjects complete 18 months of treatment. After full randomization, all study subjects will stop treatment only in the event of futility.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

A group sequential design will be used for the Mild to Moderate AD cohort. This design includes 3 looks, 2 interim looks (when 60% and 80% information fractions are achieved) and 1 final look. Interim analyses will be performed after the MCI/Prodromal cohort crosses the early success boundary. The corresponding efficacy boundaries will be 0.076, 0.022, and 0.0423 for the first, second, and final analyses, respectively. If the actual information fraction during the interim analyses is different from 60% or 80% at the interim, the efficacy boundaries will be adjusted based on the actual information fraction. If early success in the MCI/Prodromal cohort is not achieved before the final analysis that is performed when all subjects have completed 18 months treatment, then only a final analysis will be performed in mild to moderate AD subjects. In the event of futility in the MCI/Prodromal cohort, an analysis will be performed for the Mild to Moderate AD cohort based on the data for mild to moderate AD subjects available at that time. (revised per Amendment 01)

**Adaptive Randomization in the MCI/Prodromal Cohort**

Randomization to placebo or 1 of 3 dose groups of E2609 will be fixed for the first 100 MCI/Prodromal subjects randomized in the study (1:1:1:1; placebo to each of the 3 active doses for the first 100 MCI/Prodromal subjects randomized, including those randomized from both Stage A and Stage B). Thereafter, randomization probabilities to each treatment group will be updated at each interim analysis, such that the randomization probability will be increased for the placebo group and dosage groups that represent the potential target dose ($ED_{90}$), and simultaneously decreased for other active arms. (revised per Amendment 01)

**Randomization in the Mild to Moderate AD Cohort** (revised per Amendment 01)

In Stage A, the mild to moderate AD subjects will be randomized to placebo or 1 of 3 E2609 dose groups (5, 15, and 50 mg of E2609) at a 1:1:1:1 ratio, while in Stage B, the mild to moderate AD subjects will be randomized to placebo or 1 of 2 E2609 dose groups (15 and 50 mg E2609) at a 1:1:1 ratio. (revised per Amendment 01)

**Stratification** (revised per Amendment 01)

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

**Sample Size Rationale**

***Sample Size Rationale in the MCI/Prodromal cohort***

Primary endpoint – derived ADCOMS: The sample size and design characteristics to test the hypothesis for the primary objective based on the primary endpoint were determined by means of simulations. Extensive study simulations have shown that a total of 500 subjects will be sufficient to demonstrate that the most likely $ED_{90}$ dose achieves a 25% improvement over placebo with a probability of at least 80% in the interim and final analyses. There is at least a 90% probability of study success for the dose response scenarios where treatment was considered to have a clinically meaningful treatment effect. Simulations have also shown that if there is no obvious dose effect, the probability of falsely claiming superiority to placebo is at most 5%.

For each of the 4 treatment groups (3 active doses and placebo), the final number of subjects per group will differ depending on the observed interim treatment responses.

vMRI: The null hypothesis is that there is no difference between active dose and placebo. There are 3 null hypotheses corresponding to 3 active doses. The alternative hypothesis is that at least 1 null hypothesis is false (1-sided). The null hypotheses will be tested using Dunnett's method with 1-sided

alpha of 0.05. The statistical power was estimated through simulation for a moderate dose-response assumption that the percent reduction in change from baseline of total hippocampal volume compared with placebo would be 15%, 20%, and 25% corresponding to the 3 doses, respectively. The estimated power for actual planned study sample size is 78% at 18 months assuming an attrition rate of 20% at 18 months. Under a stronger dose-response assumption (ie, the percent reduction in change from baseline of total hippocampal volume compared with placebo is twice as much as that in the moderate dose-response assumption), the estimated power is at least 99% at 18 months.

Amyloid PET: The null and alternative hypotheses and statistical test are the same as those for vMRI. To estimate the sample size for the amyloid PET imaging subgroup at 18 months, a common SD of change from baseline was estimated at 0.33 and a reasonable mean difference between treatment and placebo was estimated as 0.25 (standardized uptake value ratio [SUVR]). Assuming a moderate dose-response, the best dose would achieve a difference of 0.25 (SUVR) and the middle and low doses would achieve a difference of 0.2 and 0.15 (SUVR), respectively, it would require a total of 100 subjects from all 4 arms at 18 months to achieve 80% power.

***Sample Size Rationale for the Mild to Moderate AD Cohort*** (revised per Amendment 01)

ADCOMS at Month 18: The null hypothesis is that there is no difference between active dose and placebo. There are 2 null hypotheses corresponding to 2 active doses. The alternative hypothesis is that at least 1 null hypothesis is false. The null hypotheses will be tested using Dunnett's test with 2-sided alpha of 0.05 as described for the Mild to Moderate AD cohort in the secondary analysis section. The statistical power was estimated through simulation for the dose-response assumption that the percent reduction in change from baseline of ADCOMS at 18 months compared with placebo would be 33% and 50% corresponding to the 2 doses, respectively. The estimated power for the actual planned 200 mild to moderate AD subjects is approximately 80% assuming a 2-sided alpha of 0.05. (revised per Amendment 01)

# 3 TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES



## LIST OF IN-TEXT FIGURES



## LIST OF APPENDICES

# 4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| Aβ | amyloid β |
| Aβ(1-x) | amyloid β (1-x) (ie, the amyloid β monomer from amino acid 1 to x [eg 1-42]) |
| AChEI | Acetylcholinesterase inhibitor |
| AD | Alzheimer's disease |
| ADAS-cog | Alzheimer's Disease Assessment Scale - cognitive subscale |
| ADCOMS | Alzheimer's Disease Composite Score |
| AE | Adverse Event |
| ApoE | Apolipoprotein E |
| AUC | area under the concentration x time curve |
| $AUC_{(0\text{-}24h)ss}$ | area under the concentration x time curve at steady state from time zero to 24 hours |
| BACE1 | Beta-amyloid converting enzyme 1 |
| BP | blood pressure |
| bpm | beats per minute |
| CBB | CogState Brief Battery |
| CBC | complete blood count |
| CBP | childbearing potential |
| CDR | Clinical Dementia Rating |
| CES2 | carobxyesterase-2 |
| CFR | Code of Federal Regulations |
| $C_{max,ss}$ | maximum plasma concentration at steady state |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| CRA | clinical research associate |
| CRF | case report form |
| CRO | contract research organization |
| CSF | cerebrospinal fluid |
| $C_{ss,av}$ | average steady-state concentration |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CTA | Clinical Trial Agreement |
| CYP | cytochrome P450 |
| $d_{Max}$ | Maximum effective dose |
| DSMB | data safety monitoring board |
| ECG | electrocardiogram |

| Abbreviation | Term |
|---|---|
| eCRF | electronic case report form |
| ED | early discontinuation |
| $ED_{90}$ | lowest effective dose that achieves 90% of the greatest treatment effect |
| ELISA | enzyme-linked immunosorbent assay |
| FAQ | Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire) |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FLAIR | fluid-attenuated inversion recovery |
| GCP | Good Clinical Practice |
| GDS | Geriatric Depression Scale |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |
| HCVAb | hepatitis C virus antibody |
| HSV | herpes simplex virus |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ID | identifier |
| IEC | Independent Ethics Committee |
| Ig | immunoglobulin (eg, IgA, IgG, IgM) |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISLT | International Shopping List Task |
| IxRS | interactive voice and web response system |
| LLN | lower limit of normal |
| LNH | low/normal/high |
| LP | lumbar puncture |
| MAD | multiple ascending dose |
| MCI | mild cognitive impairment |
| MCI/Prodromal | Mild Cognitive Impairment due to Alzheimer's Disease/ Prodromal Alzheimer's Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mild to moderate AD | mild to moderate dementia due to Alzheimer's Disease |
| miRNA | micro-ribonucleic acid |
| MMRM | mixed-effects model with repeated measures |

| Abbreviation | Term |
|---|---|
| MMSE | Mini Mental State Examination |
| MRI | magnetic resonance imaging |
| NAT2 | N-acetyltransferase 2 |
| NIA-AA | National Institute on Aging-Alzheimer's Association |
| OF | O'Brien-Fleming |
| PBMC | peripheral blood mononuclear cell |
| PD | Pharmacodynamic(s) |
| PET | positron emission tomography |
| PGx | pharmacogenomic(s) |
| PK | pharmacokinetic(s) |
| PP | per protocol |
| PRN | Pro re nata |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| p-tau | phosphorylated-tau |
| QD | once daily |
| QTc | corrected QT interval |
| QTcF | QTc interval calculated using Fridericia's formula |
| R | randomization |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reaction |
| SUVR | standardized uptake value ratio |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |
| TEMAV | treatment-emergent markedly abnormal laboratory values |
| t-tau | total tau |
| ULN | upper limit of normal |
| UNS | unscheduled |
| vMRI | volumetric magnetic resonance imaging |
| WHO DD | World Health Organization Drug Dictionary |
| β-hCG | beta-human chorionic gonadotropin |

# 5 ETHICS

## 5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA][s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigators or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

## 5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (CFR) (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

- European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved European Union member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

## 5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject and the identified caregiver or informant, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or understand it or if the identified caregiver or informant is unable to read, an impartial witness should be present during the entire informed consent discussion. If, in the Investigator's opinion, a subject lacks capacity to consent, the subject's assent should be obtained in addition to the written informed consent of a legal representative (capacity to consent and definition of legal representative should be determined in accordance with applicable local laws and regulations). (revised per Amendment 01) After the ICF and any other written information to be provided to subjects is read and explained to the subject and the identified caregiver or informant, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified caregiver or informant should also consent to supporting the subject's participation in the study and will be provided with a separate written ICF for his or her participation in the study, to be signed before he or she participates in any further aspects of the study.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified caregiver or informant must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified caregiver or informant will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified caregiver or informant should be

informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

All subjects will also be asked to provide written consent for cerebrospinal fluid (CSF) sampling at Baseline and after receiving study drug for 4 weeks and 18 months (or at Early Discontinuation). This consent for CSF sample collection is not required for study eligibility. (revised per Amendment 02)

# 6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 125 investigational sites globally (40 sites in the United States for Stage A and 125 sites globally for Stage B). (revised per Amendments 01 and 02)

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

# 7 INTRODUCTION

At this time, there is no cure for Alzheimer's disease (AD), no known way of slowing down the progression of this disease, and no approved treatment available to reverse the deterioration. There is, therefore, an urgent unmet medical need for drugs that slow or prevent disease progression. Beta-amyloid converting enzyme 1 (BACE1) is a key enzyme responsible for the production of amyloid β (Aβ) peptides and plaque formation, and several reports have described elevated levels of BACE1 in AD brains (Coulson, et al., 2010, Lu, et al., 2012). Once amyloid plaques form, Aβ causes BACE1 levels to increase further, thus accelerating Aβ generation and plaque growth via a positive feedback loop. Therefore, BACE1 is a promising target for modifying or treating AD.

It is now widely accepted that mild cognitive impairment (MCI) due to AD and mild to moderate AD dementia are stages on a single disease spectrum, which follows an Alzheimer's pathological cascade. (revised per Amendment 01) Recent consensus papers from the international workgroups of the National Institute on Aging-Alzheimer's Association (NIA-AA), have endorsed this hypothesis (Albert, et al., 2011; Jack, et al., 2011; McKhann, et al., 2011; Sperling, et al., 2011).

From a clinical standpoint, demonstration of an effect on slowing disease course is hampered by the lack of sensitive tools for detecting relatively small changes in progression or treatment effect especially in early disease. In addition, drugs that are expected to slow disease progression require longer study durations to ensure adequate separation from placebo. These challenges have resulted in the use of biomarkers as surrogates for clinical effect in Phase 2 studies, in order to facilitate the development process for disease modifying agents. However, subsequent Phase 3 AD studies based solely on biomarker findings in Phase 2 have failed to show clinical effect, due, in part, to the fact that biomarkers may not predict clinical outcomes for potential disease modifying agents. These findings underscore the need for innovative approaches to clinical study design for measuring the effect of treatment.

E2609 is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, E2609 inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in cerebrospinal fluid (CSF) and plasma (rat, guinea pig, and monkey). In humans, E2609 has been shown to inhibit BACE1 enzyme activity in CSF and lower the levels of Aβ, including amyloid beta monomer from amino acid 1 to x (Aβ[1-x]), Aβ(1-40) and Aβ(1-42), in CSF both in vitro and in vivo. See the Investigator's Brochure for additional information. The target indication for E2609 is therefore treatment and disease modification of AD.

The present clinical study represents the sole Phase 2 study for the E2609 program, and is designed to establish Proof of Concept in subjects with Mild Cognitive Impairment due to Alzheimer's Disease/Prodromal Alzheimer's Disease (referred to as MCI/Prodromal throughout the protocol). The study also allows investigation of efficacy in subjects with mild to moderate dementia due to Alzheimer's Disease (referred to as mild to moderate AD throughout the protocol) to determine whether the effects of E2609 in this later stage population are comparable with those established in the MCI/Prodromal population within

this same study. (revised per Amendment 01) In the MCI/Prodromal population, Bayesian response adaptive randomization design is used with frequent interim analyses to continually update randomization allocation based on emerging clinical endpoint data. This approach allows for ongoing assessment of drug futility or evidence of early success and can mitigate the risks associated with larger and longer studies required to demonstrate clinical efficacy by leading to more efficient study termination or early advancement to a Phase 3 program. Results from this study will guide both the decision to move into Phase 3 development and the selection of the dose strengths to be taken into Phase 3. Moreover, this study is intended to be supportive for registration in the MCI/Prodromal population.

In the MCI/Prodromal population, this study will compare placebo and 3 oral doses of E2609 (5, 15, and 50 mg) administered once daily (QD) for 18 months. In the mild to moderate AD population, this study will compare placebo and 2 oral doses of E2609 (15 and 50 mg) administered QD for 18 months. To date, the longest duration of dosing with E2609 is 14 days (multiple ascending dose [MAD] Study E2609-A001-002 [Study 002]). (revised per Amendment 01)

This study (E2609-G000-202 [Study 202]) will comprise 2 stages: Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 in the United States sites only, before expanding enrollment to a larger and more global population of subjects in Stage B. This design will allow close monitoring of safety by an independent data safety monitoring board (DSMB), including a formal safety review as soon as the first 60 randomized subjects have completed 12 weeks of treatment, have discontinued study drug or have withdrawn from the study. The study also includes a number of exclusion criteria, specific blinded safety monitoring procedures and safety criteria for discontinuation of study drug in light of the preclinical and clinical safety data collected to date following administration of E2609.

## 7.1 Nonclinical and Clinical Safety Data

The toxicity of E2609 has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomologus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by E2609 in a clinical setting. Further details of the nonclinical data to date with E2609 can be found in the Investigator's Brochure.

The clinical program to date includes 6 Phase 1 studies:

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, single ascending dose (SAD) study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50-mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled MAD study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the pharmacokinetic (PK) levels of E2609 and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of E2609. It also investigated the effects of E2609 on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [$^{14}$C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of E2609 under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) was a randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with E2609. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with E2609. In elderly subjects treated with 50 mg of E2609, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTc interval calculated using Fridericia's formula (QTcF) from baseline (14.9 msec at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of E2609 might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that E2609 altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of E2609. A single dose of E2609 up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, E2609 administered at doses of 200 and 400 mg was associated with

reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of E2609 on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP3A4] and carboxyesterase-2 [CES2]) increased by approximately 70% the area under the concentration × time curve (AUC) of E2609. Consequently, strong inhibitors of CY3A4 will be prohibited in this study.

Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of E2609. Therefore, no restrictions are required for the use of concomitant medications which are known to be inducers of CYP450 enzymes. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of E2609 when coadministered with E2609 but not when dosed at least 2 hours apart from E2609. E2609 (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of E2609. Therefore, on the basis of drug interaction considerations, the only restriction of concomitant medications is that for strong inhibitors of CYP3A4.

# 8 STUDY OBJECTIVES

## 8.1 Primary Objectives

The primary objectives are:

1. To evaluate the efficacy of daily dosing with 3 doses of E2609 compared with placebo by establishing the lowest effective dose that achieves 90% of the greatest treatment effect ($ED_{90}$) for E2609 on the derived Alzheimer's Disease Composite Score (ADCOMS) at 18 months of treatment in subjects with MCI/Prodromal
2. To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with mild to moderate AD (revised per Amendment 01)

## 8.2 Secondary Objectives

The secondary objectives are: (revised per Amendment 02)

1. To evaluate the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects, as measured by volumetric magnetic resonance imaging (vMRI)
2. To evaluate the efficacy of E2609 compared with placebo on the derived ADCOMS at 18 months in mild to moderate AD subjects (revised per Amendment 01)

## 8.3 Exploratory Objectives

(revised per Amendments 01 and 02)

The exploratory objectives are:

1. To explore the effect of E2609 compared with placebo on the derived ADCOMS following 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
2. To explore the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in mild to moderate AD subjects, as measured by vMRI
3. To explore the effects of E2609 compared with placebo on Aβ(1-x) and Aβ (1-42) in CSF after 4 weeks and 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects (revised per Amendment 02)

4. To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during posttreatment follow-up, in MCI/Prodromal and mild to moderate AD subjects, by assessment of:
   a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
   b. The Clinical Dementia Rating (CDR) scale
   c. The Mini-Mental State Examination (MMSE)
   d. The CogState Brief Battery (CBB)
   e. The Functional Assessment Questionnaire (FAQ; (also known as the Functional Activities Questionnaire)
   f. The International Shopping List Task (ISLT)
5. To explore the effects of E2609 compared with placebo on various biomarkers in MCI/Prodromal and mild to moderate AD subjects. Biomarkers to be explored include:
   a. CSF biomarkers of neurodegeneration (eg, tau, phosphorylated-tau [p-tau]) after 18 months of treatment
   b. Plasma and CSF amyloid, and CSF BACE1 measurements during 18 months of treatment and during posttreatment follow-up
   c. vMRI measurements including left and right hippocampal volume, whole brain volume, and total ventricular volume at 6, 12, and 18 months of treatment and during posttreatment follow-up
   d. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)
6. To characterize the population PK of E2609 in MCI/Prodromal and mild to moderate AD subjects, and to examine the effect of intrinsic and extrinsic factors (including N-acetyltransferase 2 [*NAT2*] phenotype) on the PK
7. To explore the relationship between the treatment effects of E2609 on the ADCOMS and its effects on CSF amyloid, CSF BACE1, CSF tau, and vMRI in MCI/Prodromal and mild to moderate AD subjects

# 9 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan

Study 202 is a multicenter placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild to moderate AD. (revised per Amendment 01)

A common set of inclusion criteria, consistent with the NIA-AA clinical research criteria for MCI due to AD or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study will be conducted in 2 stages, Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 (at least 12 weeks) before expanding enrollment to include a larger number of subjects in Stage B. All MCI/Prodromal subjects will be included in the primary efficacy evaluation irrespective of whether they were recruited into Stage A or Stage B. Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B. All mild to moderate AD subjects will be included in the efficacy evaluation of that cohort. (revised per Amendment 01)

Both Stage A and Stage B will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days, plus an additional window of up to 30 days if required [revised per Amendment 02]) will consist of a Screening Visit and a Baseline Visit. Screening assessments will be organized into 4 tiers; see Section 9.5.2.2, Table 6, and Figure 2.

All screening assessments must be completed, and eligibility to continue to the Baseline Period confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

In Stage A, all subjects (MCI/Prodromal and mild to moderate AD) will be randomized 1:1:1:1 to 4 treatment groups (E2609 at 3 doses or placebo). In Stage B, randomization of MCI/Prodromal subjects will start off at a 1:1:1:1 ratio (E2609 at 3 doses or placebo), until a total of 100 MCI/Prodromal subjects have been randomized. Remaining subjects in the MCI/Prodromal cohort will be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. Subjects with mild to moderate AD who are recruited in Stage B will be randomized in a 1:1:1 ratio to 3 treatment groups (E2609 at 2 doses or placebo). (revised per Amendment 01)

An overview of the study design is presented in Figure 1 .

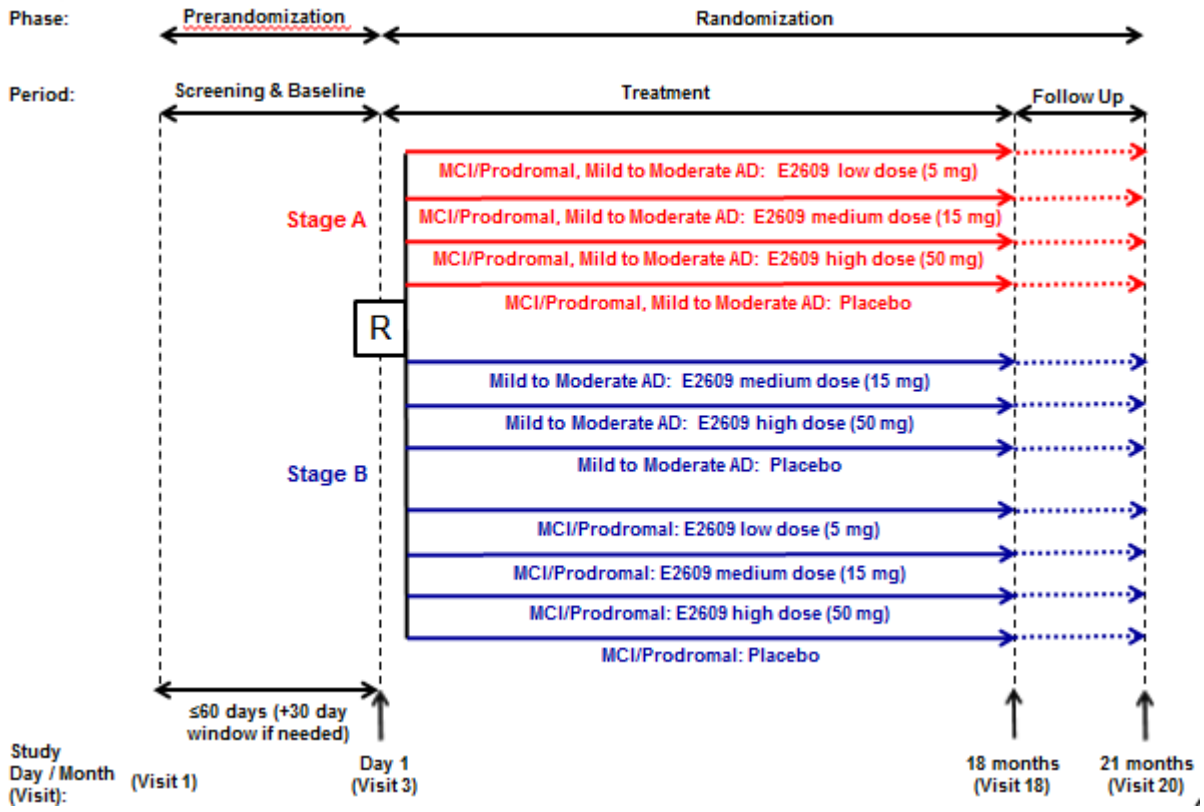



**Figure 1 Design of Study E2609-G000-202**

**(revised per Amendments 01 and 02 )**

R = randomization.

### Stage A

Stage A will be limited to approximately 40 sites in the United States. (revised per Amendments 01 and 02) Stage A will randomize 60 eligible subjects at Visit 3, 1:1:1:1 to 4 treatment groups within each clinical cohort. (revised per Amendment 01) There will be no Bayesian adaptation during Stage A. In addition to the placebo group, 3 doses of E2609 will be used to reduce CSF Aβ levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/PD modeling shows these doses should achieve these targets when administered QD with food and will be evaluated based on the 4-week assessment of CSF Aβ(1-x) from subjects who provide voluntary consent for CSF measurement. (revised per Amendment 02) (see Section 9.4.4).

During Stage A, safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the first subject is randomized during

Stage A, an independent DSMB (including at least 1 immunologist) will review all safety data in an unblinded manner. The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. Unless the DSMB recommends otherwise, randomization of subjects into Stage A will continue until 60 subjects have been randomized and dosed. (revised per Amendment 01)

Interim analyses of the E2609 PK and PD profiles will be performed on subjects who consent to provide CSF samples at Baseline and after 4 weeks of study drug. These data will be used to evaluate the CSF PD effects of E2609 doses, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels (see Section 9.4.4). (revised per Amendments 01 and 02) The mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment for each dose of E2609 and its 90% confidence interval will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data from Stage A and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline after 4 weeks of dosing. (revised per Amendment 02)

Once 60 subjects in Stage A have completed at least 12 weeks of treatment (or discontinued study drug early) an interim safety analysis will be conducted by Eisai and the DSMB. (revised per Amendment 01) Subjects in Stage A will continue study drug while the DSMB reviews all the available safety data, but randomization of additional subjects will not take place (ie, recruitment into Stage B will not commence) until the safety analysis is completed by the DSMB. At the time of this interim safety analysis, some subjects will have more than 12 weeks of safety data.

If there are safety signals with one of the E2609 dose groups that would require dose adjustment, changes to dose will be reflected in an amendment to the protocol. Information on how these subjects will be handled in the primary analysis will be described in the Statistical Analysis Plan.

**Stage B**

Stage B will start after the DSMB safety review of Stage A has shown acceptable safety and tolerability of E2609 and after the doses of E2609 to be used in Stage B are evaluated. (revised per Amendment 02) Based on data from Stage A, the protocol will be reviewed and may be amended before beginning Stage B. Safety data from Stage B will continue to be reviewed by the DSMB (approximately every 3 months) until recruitment in the study is completed; following this the DSMB will meet approximately every 6 months.

Stage B will be conducted globally and will enroll, randomize, and dose additional eligible subjects up to a maximum of 500 MCI/Prodromal subjects and up to a maximum of 200 mild to moderate AD subjects. The final total number of MCI/Prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. (revised per Amendment 01)

In Stage B, both cohorts will include separate placebo groups. The MCI/Prodromal cohort will include 3 doses of E2609 (5, 15, and 50 mg QD), whereas the Mild to Moderate AD cohort will only include 2 doses of E2609 (15 and 50 mg QD). (revised per Amendment 01)

Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort during Stage B. Randomization of MCI/Prodromal subjects into Stage B will commence according to a fixed schedule (1:1:1:1; placebo:5 mg E2609:15 mg E2609:50 mg E2609) until a total of 100 MCI/Prodromal subjects (including those from Stage A) have been randomized. (revised per Amendment 01) The remaining subjects in the MCI/Prodromal cohort in Stage B will then be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. The mild to moderate AD subjects will be randomized according to a fixed schedule (1:1:1 placebo; 15 mg E2609; 50 mg E2609) throughout Stage B. (revised per Amendment 01)

Interim efficacy analyses are planned and are discussed in Section 9.7.3.

### 9.1.1 Prerandomization Phase

The Prerandomization Phase includes a Screening Visit and a Baseline Visit. All Screening Visit assessments must be completed and eligibility to progress must be confirmed before any Baseline Visit assessments are performed. All Screening Visit and Baseline Visit assessments must be completed within 50 days (plus an additional window of up to 30 days if required [revised per Amendment 02]) and a window of no more than 10 days is to be observed between the completion of all Baseline Visit assessments (including confirmation of eligibility following all Baseline Visit assessments) and randomization into the study at Visit 3 (revised per Amendment 02). Thus, the Prerandomization Phase will last for up to 60 days, plus an additional window of 30 days if required (revised per Amendment 02). The series of assessments conducted during this phase will determine eligibility for randomization into the study.

Inclusion criteria are discussed in Section 9.1 and detailed in Section 9.3.1. Before randomization the clinician will provide a judgment on the classification of a subject as either MCI/Prodromal or likely mild to moderate AD. (revised per Amendment 01) This judgment may be discussed and reviewed with the Sponsor or Sponsor's representative, as necessary.

Results of the Screening safety magnetic resonance imaging (MRI) will be valid for 90 days from the date of scanning. Results of the lumbar puncture (LP) from subjects who voluntarily consent for CSF measurement will be valid for 90 days from the date of testing. Results of Screening PET scans conducted specifically for this study and for use in the longitudinal analyses will also be valid for 90 days from the date of scanning. These assessments will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. Historical PET scans used for determination of eligibility only (ie, not used for the longitudinal analyses) are valid for 12 months. (revised per Amendment 02)

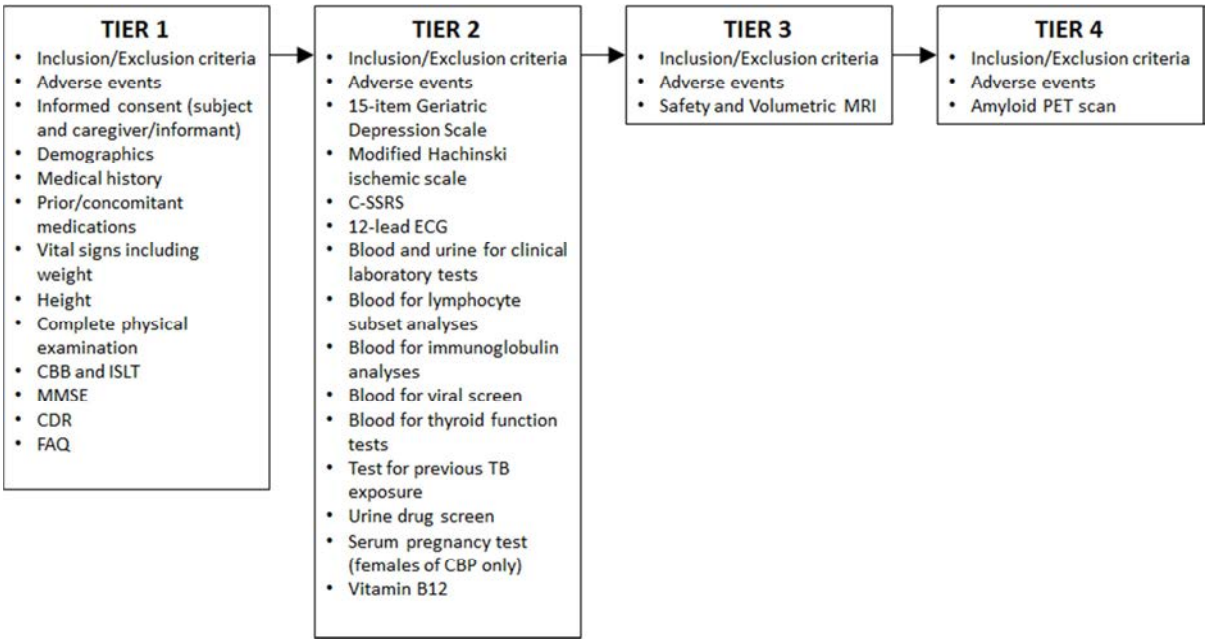
#### 9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and caregiver or informant, and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained from both the subject and the caregiver or informant. The caregiver or informant needs to be present at this visit.

Study site personnel will interview the subject and caregiver or informant to obtain demographic and clinical information as described in Table 6, and will review inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2 and perform any required assessments in order to complete these criteria. Prior medications and medications currently being taken by the subject will be reviewed (see Section 9.4.7). The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

Clinical assessments for eligibility will be conducted during the Screening Visit as described in Table 6 and Figure 2.

Every effort should be made to conduct these assessments in the morning, but if this is not possible, they should be conducted at the same time of day at all subsequent visits. The screening assessments/procedures have been organized into 4 distinct tiers (Table 6 and Figure 2). All assessments/procedures in each tier should be completed, and eligibility to continue screening in the study confirmed, before any assessments/procedures from the next tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures as long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. (revised per Amendment 01)




## Figure 2 Assessments to be Performed at Screening by Tier

CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), ISLT = International Shopping List Task (immediate and delayed recall), MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PET = positron emission tomography, TB = tuberculosis.

Cognitive assessments (Tier 1) are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). The recommended order of assessments at Screening is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. (revised per Amendment 02) The investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session (Tier 3).

Amyloid PET imaging will be used to confirm all subjects have amyloid deposition in the brain (Tier 4). An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. If an historical amyloid positive PET scan is being used, it should be submitted to the central PET reading group after the subject has completed and passed all Tier 1 assessments. (revised per Amendment 02)

#### 9.1.1.2 Baseline Period

All Screening Visit assessments must be completed (and eligibility to progress confirmed) before any Baseline Visit assessments are performed. The Baseline Visit assessments (per Table 6 and Section 9.5.1.2) are to be completed as soon as possible after completion of the final Screening Visit assessment (ie, PET scan) such that all Screening Visit and Baseline Visit assessments are completed within 50 days, plus an additional window of up to 30 days if required. (revised per Amendment 02)

Inclusion and exclusion criteria will again be reviewed, vital signs including weight will be recorded, and a 12-lead ECG will be conducted in triplicate. A routine physical examination will be conducted and a dermatological assessment and neurological examination will be performed. A urine pregnancy test will be conducted for females of childbearing potential. Blood will be collected from all subjects for clinical chemistry and hematology, lymphocyte subset analyses, Ig analyses, and PD assessments. Blood samples will be collected and stored for determination of a subject's previous exposure to infective pathogens in the event of AEs that warrant further investigation occurring at a later point in the study. Psychometric assessments will be administered to the subject in the order stated in Table 6. The caregiver or informant needs to be present at this visit. The Columbia Suicide Severity Rating Scale (C-SSRS) will also be administered (Section 9.5.1.5.11).

For subjects who consent to CSF sample collection, CSF will be obtained at this visit for PK and PD assessments (see Section 9.5.1.5.3). (revised per Amendment 02)

Blood will be collected from all subjects for pharmacogenomic (PGx) analyses of apolipoprotein E (*ApoE*) and the *NAT2* phenotype of subjects enrolled in the study (see Section 9.7.1.7.2).

### 9.1.2 Randomization Phase

Subjects who complete the Baseline Visit assessments, and are eligible based on the inclusion and exclusion criteria (see Section 9.3.1 and Section 9.3.2), will begin the Randomization Phase no more than 10 days after completion of the Baseline Visit assessments and confirmation of the eligibility of the subject based on the results of all the Baseline Visit assessments (revised per Amendment 02).

The Randomization Phase will consist of a Treatment Period of 78 weeks duration and a Follow-Up Period of 12 weeks after the last dose of study drug.

#### 9.1.2.1 Treatment Period

Subjects will be randomized at the beginning of the Treatment Period and will receive study drug or placebo, to be administered orally QD with food. Double-blinding to study drugs will be in effect throughout the Treatment Period. The dose for a subject will not be changed during the study. However, dose adjustment for Stage B may be considered and subjects already randomized to a dose that needs to be adjusted will be switched to continue their treatment at the new adjusted dose.

Safety criteria for discontinuation of study drug are detailed in Section 9.3.3.

Subjects will attend the study site every week for the first 4 weeks after beginning study drug, then fortnightly until 12 weeks have elapsed since first dose. Visits will then be conducted at 16, 20, 26, 39, 52, 65, and 78 weeks after the first dose.

#### 9.1.2.2 Early Discontinuation

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug.

Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie. at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB and ISLT) will be conducted. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) after the Early Discontinuation Visit or within ± 8 days of either of the Follow-Up Visits (Visit 19 and Visit 20). Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

#### 9.1.2.3 Follow-up Period

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug (Visit 19) and a second 12 weeks after the last dose of study drug (Visit 20). If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the posttreatment Follow-Up period.

The end of the study will be defined as the date of the clinical database lock (ie, when all study data are collected and data validation is completed).

As required by some regulatory agencies, the following estimates are provided:

- The study will begin in Nov 2014 and is projected to end by Oct 2019 (end date will depend on actual recruitment rate).
- The maximum estimated period for each subject on study is anticipated to be approximately 2 years.

## 9.2 Discussion of Study Design, Including Choice of Control Groups

### 9.2.1 Overview

The 2 stage design of the study allows for the safety and tolerability of E2609 to be assessed in a limited number of subjects (n=60) before expanding recruitment into a larger population of subjects. (revised per Amendment 01)

The design of this study allows Proof of Concept to be established in subjects with MCI/Prodromal AD. The study also allows investigation of efficacy in subjects with mild to moderate AD to determine whether the effects of E2609 in this later stage population are comparable with those established in the MCI/Prodromal population within this same study (see Section 9.2.3 for discussion of the Bayesian design used in this study). (revised per Amendment 01)

The inclusion criteria for the MCI/Prodromal cohort will be consistent with the NIA-AA criteria for MCI due to AD (Albert, et al., 2011) and with the definition of Prodromal AD per Dubois et al., 2010 (see Section 9.2.2).

There is no active or positive control for this study as at this time, there is no cure for AD, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary efficacy tool for this Proof of Concept study is the composite scale ADCOMS (change from baseline in the derived ADCOMS at 18 months). The ADCOMS (Hendrix, et al., 2012) represents a novel composite approach integrating components of well-established tools (ADAS-cog, MMSE, and CDR) to improve sensitivity to disease progression and treatment effects in subjects with AD (see Section 9.2.4).

Secondary efficacy endpoints include a biomarker of neuronal degeneration (shrinkage of neurons), which is the change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI; and a cognitive and functional assessment, which is the change from baseline in the derived ADCOMS at 18 months of treatment in mild to moderate AD subjects. (revised per Amendments 01 and 02) Exploratory endpoints including assessments of efficacy, safety and other biomarkers are also included.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

The rationale for the selection of doses used in the study is provided in Section 9.4.4.

### 9.2.2 Rationale for Study Population

By the time AD progresses to dementia, with loss of functional capabilities, the amyloid load in the brain is approaching a plateau and significant neurodegeneration has occurred (Jack, et al., 2010). Consequently, there is a growing view within the AD field that it may be necessary to initiate disease modifying treatments earlier, before the onset of clinical dementia (Aisen, et al., 2010). However, this hypothesis remains to be demonstrated with clinically effective therapies, and may not apply to all therapeutic classes, it is possible that this consideration explains the failure of the humanized monoclonal antibody bapineuzumab

(which targeted brain amyloid) to demonstrate clinical efficacy in late-phase studies in mild to moderate AD dementia. (revised per Amendment 01)

With this consideration taken into account, the primary clinical population of focus in this study is subjects with MCI/Prodromal AD. The mechanism of action of a BACE1 inhibitor where amyloid production is reduced means E2609 is more likely to be efficacious (ie, slow disease progression) the earlier in disease progression treatment is started, where limited neurodegeneration has occurred and associated clinical deficits are at a minimum. However, since the effect of BACE1 inhibition along the AD continuum remains to be characterized, E2609 will also be evaluated for its profile in mild to moderate stages of AD, in the event data emerge supporting its use beyond MCI/Prodromal AD. Indeed, recent data support the notion of continued progression of amyloid pathology even in these later stages of the disease (Hu, et al., 2015), although at a slower pace, suggesting a positive effect of BACE inhibition and amyloid beta reduction cannot be ruled out even in the later stages of the disease trajectory. Hence, in this study, E2609 will be assessed in subjects with disease states ranging from MCI/Prodromal to mild and even moderate AD. (revised per Amendment 01)

As discussed, efficacy is more likely to be observed in subjects with MCI/Prodromal AD but there is the possibility that efficacy will also be evident following administration of an amyloid modifying agents such as E2609 in subjects with more advanced disease such as mild to moderate AD. (revised per Amendment 01) For example, a study of tarenflurbil, a selective Aβ(1-42)-lowering agent, on cognition and function in subjects with mild to moderate AD showed the subjects with mild AD had lower rates of decline than those in the placebo group in activities of daily living and global function; however, slowing of cognitive decline did not differ significantly (Wilcock, et al., 2008). Similarly, differential effects on cognitive measures have been observed with solanezumab, where some benefit from treatment was observed in subjects with mild AD, although studies with solanezumab were considered to have failed to improve cognition or functional ability significantly (Doody, et al., 2014). Therefore, it is relevant to compare the effect of the BACE1 inhibitor E2609 in 2 different subject populations that differ in terms of AD severity before the initiation of large Phase 3 clinical studies. (revised per Amendment 01)

### 9.2.3 Rationale for the Use of Bayesian Adaptive Design

This study uses a Bayesian adaptive design for the MCI/Prodromal cohort only in Stage B. This design optimizes subject allocation and evaluation of efficacy in a smaller number of subjects by maximizing the number of subjects exposed to doses of interest. Frequent interim analyses will be performed to assess the probability of early success and futility and to aid in making early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis, such that subjects are more likely to receive a dose that is efficacious.

Subjects with mild to moderate AD will be assessed as a "nested" population that does not follow the Bayesian adaptive design. It was not considered appropriate to have a Bayesian design for both cohorts as this would have substantially increased the overall study sample size, delayed analyses of dose response, and would have added background "noise" for the

comparison of subjects with MCI/Prodromal AD compared with those with mild to moderate AD. Data from each cohort will be analyzed independently for the purposes of decision making. A separate analysis of the 2 cohorts avoids the risk of data from subjects with mild to moderate AD confounding the results for the primary population (MCI/prodromal). (revised per Amendment 01)

### 9.2.4 Rationale for Clinical Endpoints

The ADCOMS (Hendrix, et al., 2012) was developed utilizing data from multiple studies to investigate responsiveness to progression and treatment effects rather than sensitivity to baseline deficits. The score was built empirically with no a priori assumptions, using a partial least squares regression model for placebo data from 4 MCI studies with a duration ≥12 months. A combination of cognitive and functional items was selected from a variety of well-established and validated scales that is most sensitive to change over time. The partial least squares regression coefficients from the model were used to form a weighted composite score comprising a total of 12 individual items taken from the ADAS-cog (4 items), the MMSE (2 items), and CDR (6 items), that assess both cognition and global function. Performance of the ADCOMS has been assessed against the original scales in several studies. The use of the ADCOMS allows for substantial sample size reductions in non-enriched and enriched MCI populations even over a 12-month period by increasing sensitivity. This derived score has shown adequate sensitivity in the MCI due to AD amyloid confirmed (CSF Aβ-positive) subgroup.

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007).

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The CDR is a clinical global rating scale requiring the interviewing of both the subject and an informant who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The CBB is a brief, computer-administered cognitive test battery that requires approximately 10 minutes for administration (Darby, et al., 2012; Fredrickson, et al., 2008; Maruff, et al., 2009). The CBB has been used to detect cognitive impairment in several neurodegenerative conditions including the measurement of cognitive function in healthy older adults and in

adults with clinically diagnosed AD and prodromal AD (Darby, et al., 2009; Hammers, et al., 2012; Lim, et al., 2012a; Lim, et al., 2012b). The administration, scoring, and reporting of the CBB is automated and highly standardized, resulting in cognitive paradigms that have been well-validated in neuropsychological and cognitive studies (Fredrickson, et al., 2008; Maruff, et al., 2009). See Section 9.5.1.3.1 for further details.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al,. 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials on the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson et al., 2011, Lim, et al., 2012a, Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with E2609 treatment.

Volumetric magnetic resonance imaging is discussed in Section 9.2.5.4.

## 9.2.5 Rationale for Biomarkers

### 9.2.5.1 Overall Rationale

The biomarker strategy for this study includes the following aims:

- To establish an amyloid load in the brain at study entry (via the PET eligibility inclusion criterion)
- To evaluate safety (principally by MRI)
- To evaluate a PD effect in terms of both Aβ in CSF and brain amyloid assessed by amyloid PET and to establish that this PD effect is maintained long-term (revised per Amendment 02)
- To evaluate disease modification through longitudinal assessments of vMRI, amyloid PET, and CSF biomarkers of neurodegeneration (tau and p-tau)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

### 9.2.5.2 Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect of E2609 on Aβ(1-40) +Aβ(1-42) and other C-terminally truncated Aβ peptides such as Aβ(1-38) through inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using $^{[11}C^{]}$PiB, suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The

aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases in CSF Aβ concentrations that are seen in AD are believed to be related to this decrease in brain Aβ availability.

Both total tau (t-tau) and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni and Bhaskar, 2012). CSF tau measurements have been correlated with cerebral atrophy, while their ratios with Aβ42 have provided useful predictors of cognitive decline and progression to dementia due to AD. Rebalancing dysregulated amyloid production early in the process may positively affect the neurodegenerative process and thus affect these markers and benefit the disease trajectory. Therefore, monitoring these markers in conjunction with amyloid imaging may provide further supportive evidence of efficacy.

Baseline levels of Aβ(1-42), tau, and p-tau will also help elucidate the extent of AD pathology at entry to the study and can be combined with baseline levels of *ApoE4* genotyping in addition to the baseline imaging variables to help explain differences in treatment response.

The study will be stratified at randomization for *ApoE4* gene status in order to account for any *ApoE* status by treatment interaction or *ApoE* status by amyloid-related imaging abnormalities risk interaction.

#### 9.2.5.3 Amyloid PET

Amyloid PET imaging will be used in this study for 2 primary reasons: 1) to confirm the presence of AD pathology in the brain of subjects with MCI/Prodromal AD or mild to moderate AD at entry to the study; and 2) to evaluate the effects of E2609 on amyloid levels in the brain, both by whole brain analysis (the average of 5 to 6 cortical regions) and brain region analysis. (revised per Amendment 01)

Longitudinal amyloid PET imaging will be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug) as an exploratory measure of the potential disease-modifying effects of E2609. Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses) and will only be conducted until 18-month PET scans of acceptable quality have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used. (Revised per Amendment 02)

#### 9.2.5.4 vMRI

Volumetric imaging will be used to evaluate the effects of E2609 on rates of atrophy across the different dose groups and to provide support that effective treatment is associated with modification of disease course (secondary endpoint for the MCI/Prodromal population and exploratory endpoint for the mild to moderate AD population). (revised per Amendment 01) A large body of data has shown that structural MRI reliably tracks disease progression in

AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. Clinically efficacious doses are predicted to be associated with a slowing in the rate of hippocampal atrophy compared with rates observed in the placebo and non-efficacious dose groups. Treatment effects on left and right hippocampal, whole brain, and total ventricular volumes are exploratory endpoints.

Annualized rates of change of 2% to 3% have been reported for the AD brain compared with 1% in MCI and <1% in age-matched controls (Hua, et al., 2010, Leung, et al., 2010). However, subjects with MCI due to AD-dementia (CSF Aβ <192 pg/ml or positive amyloid imaging) show rates of atrophy comparable to those observed in subjects with AD-dementia (Hua, et al., 2009; Hua, et al., 2010; Leung, et al., 2010; Morra, et al., 2009), supporting the notion that such subjects are on similar trajectories as those with mild AD-dementia. Lower levels of CSF Aβ42, amyloid positivity on PET imaging, and higher levels of CSF tau in addition to the presence of the *ApoE4* allele have all been associated with greater rates of brain atrophy (Fjell, et al., 2010a; Fjell, et al., 2010b) and will be entered as covariates in various analyses. Hippocampal atrophy has also been shown to predict clinical progression independently of amyloid levels in the brain (Jack, et al., 2010), and this measure will be entered as a covariate in the analysis of the clinical endpoints along with the aforementioned variables.

Brain volume (total ventricular volume, whole brain, temporal lobe) generally shows a modest correlation with performance on a number of cognitive scales (Hua, et al., 2009; Hua, et al., 2010; Freeborough, et al., 1997; Leung, et al., 2010). Using volumetric analysis performed at 6-month intervals, these relationships and the effects of E2609 treatment will be explored further. Recent advances in analysis software have made structural imaging more sensitive to detect small changes and able to reliably measure rates of atrophy at these intervals, particularly in the posterior parietal and the lateral temporal regions during the early stages of disease (Hua, et al., 2009; Hua, et al., 2010). Given these observations, a demonstration of significant slowing or stabilization in the rate of atrophy in response to treatment, compared with placebo, will offer further support for disease modification.

### 9.2.6 Clinical Risks and Mitigation Strategy

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, and to mitigate clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. These safety aspects include the following:

- Two-stage study design: there will be a pause in recruitment after 60 subjects have been randomized to study drug (Stage A). Only after the safety of E2609 in these first 60 subjects (consisting of up to 12 weeks data for the later subjects and longer dosing periods for the earlier subjects) has been reviewed by the DSMB and considered acceptable, will randomization of further subjects into the study commence (Stage B). (revised per Amendment 01)
- Immunology-related and infection-related exclusion criteria

- Review of unblinded safety data by an independent DSMB at regular intervals
- Safety criteria for discontinuation of study drug based on CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cell) and other lymphocytes (absolute counts and percentage change from baseline), skin rash, reoccurrence of herpes virus infections including any oral herpes, genital herpes or shingles, other infections, MRI changes, ECGs, and pregnancy.

In addition to the features above, other safety aspects of this study designed to mitigate clinical risk include the following:

- Blinded safety data will be monitored by Eisai at regular intervals during the course of the study
- Routine safety assessments will include the monitoring and recording of all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events. To assess potential immunomodulatory effects, peripheral blood mononuclear cells (PBMCs) will be collected at baseline, during treatment, and posttreatment.

As per the communication from the Food and Drug Administration (FDA) in Aug 2013, there are concerns that hypopigmentation of the skin and mucous membranes may occur with BACE1 inhibitory drugs. Although no such effects have been seen with E2609 to date, assessments by a reviewing dermatologist will be performed at regular intervals during the study. These assessments will be made centrally, using standardized photography and will specifically include evaluation of any areas of depigmentation or any rash. Dermatological assessments will be supplemented with a specific question to subjects regarding skin changes at each visit. Any such changes could be referred to the central reviewing dermatologist, and to a local dermatologist if needed, for further evaluation. See Section 9.5.1.5.8 for further details.

- Baseline and on-study blood and DNA samples will be taken and stored for all subjects, and CSF samples will be taken and stored for all subjects who consent to CSF sample collection (revised per Amendment 02). These samples may be tested in the event that a subject develops AEs that warrant further investigation (eg, if a subject develops a treatment-emergent infection) (see Section 9.5.1.2.2).
- Central reading of safety brain MRI assessments (including any MRI evidence of demyelination) will be performed at Screening, at approximately 6-month intervals during the Treatment Period, and at the final Follow-Up Visit.
- Full neurological examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations. Details of the neurological examination are given in Section 9.5.1.5.9.

- Cognitive decline will be assessed as a safety assessment (ADAS-cog$_{14}$, MMSE, and CBB). Of particular importance will be the assessment of reaction time testing using the detection and identification tasks on the CBB.
- An assessment of suicidality using the C-SSRS will be performed at Screening, Baseline, and at regular intervals during the Treatment and Follow-Up Period (see Section 9.5.1.5.11).
- All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will have at least 2 off-treatment Follow-Up visits (4 and 12 weeks after the last dose of study drug). More frequent safety assessments can be made as unscheduled assessments/visits during the off-treatment Follow-Up period, if clinically indicated.
- An ophthalmic examination will be conducted at Baseline and if the subject experiences visual disturbances during the course of the study (see Section 9.5.1.2.1).

## 9.3 Selection of Study Population

Stage A will randomize 60 eligible MCI/Prodromal or mild to moderate AD subjects at approximately 40 sites in the United States (revised per Amendment 02). There will be no restriction to the number of subjects from either population. Stage B will randomize subjects at approximately 125 sites globally. Recruitment will continue in Stage B until a maximum of approximately 500 MCI/Prodromal subjects and up to a maximum of approximately 200 mild to moderate AD subjects have been randomized (including subjects randomized during Stage A). The final total number of MCI/prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. The number of mild to moderate AD subjects randomized in Stage B will depend upon the number of mild to moderate AD subjects randomized during Stage A. (revised per Amendment 01)

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

### 9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD (Albert, et al., 2011) or AD dementia (McKhann, et al., 2011) and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at Screening Visit 1:**
(revised per Amendment 02)

a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation
b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT. Alternatively, cognitive impairment of at least 0.5 SD from age-adjusted

norms in delayed recall on the ISLT plus impairment of at least 1 SD from age-adjusted norms in at least 1 other computerized learning and memory test (ISLT immediate recall, or 1 of the learning and memory components of the CBB). (revised per Amendment 02)

c. FAQ ≤24 (revised per Amendment 01)

d. MMSE ≥16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading; an historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group (revised per Amendment 02)
3. Male or female, age 50 to 85 years, inclusive at time of consent
4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.
5. If receiving acetylcholinesterase inhibitor (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the Baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.
6. Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization

### 9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or MRI
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening

4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and < 1cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could, in the opinion of the investigator, confound the MCI/Prodromal or mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendments 01 and 02)
7. A score of ≥8 on the 15-item Geriatric Depression Scale (GDS) at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the LLN for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
12. Any contraindications to LP for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity). Only applicable to subjects consenting to CSF sample collection (revised per Amendment 02)
13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of Ig deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis

16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization.
20. Any active infection within the last 4 weeks prior to randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below population-adjusted LLN at Screening or Baseline and confirmed by a repeat test conducted 1 week after the initial test. The population-adjusted LLN for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are 396, 157, and 74 cells/μL respectively. See Appendix 5. (revised per Amendment 02)
23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the Investigator and the Medical Monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of clinical immunodeficiency. The discussion with the Medical Monitor should include a detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)
24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate ECGs. A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute (bpm) at Screening or Baseline

29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.
33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo). Diagnosis of an underlying disease causing hypopigmentation is not necessary for exclusion if the clinical presentation is consistent with such a condition. Hypopigmentation associated with scarring need not be exclusionary. (revised per Amendment 02)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the C-SSRS suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation

42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period or for 28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.
    - Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.

      (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).
44. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or not practicing highly effective contraception throughout the study period or for 28 days after study drug discontinuation). No sperm donation is allowed during the study period and for 28 days after study drug discontinuation.

### 9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may discontinue study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to stop study drug or withdraw from the study at any time for any reason.

Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug (see Section 9.1.2.3). Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie, at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB and ISLT) will be conducted. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) after the Early Discontinuation Visit or within ± 8 days

of either of the Follow-Up Visits (Visit 19 and Visit 20). Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the Subject Disposition eCRF page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study drug and withdraws from the study at the same time, the ED Visit will be followed (see Section 9.5.5).

Safety-related criteria for discontinuation of study drug include the following:

a. A study drug discontinuation threshold will be set based on absolute counts of CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells). The discontinuation threshold will be set at below the level of the population-adjusted LLN (CD4=396 cells/µL; CD8=157 cells/µL; and CD19=74 cells/µL), at a level that represents a greater risk of opportunistic infection in the treated population. (revised per Amendment 02) For CD4 (T helper cells) the discontinuation threshold is 250 cells/µL. For CD8 (cytotoxic T cells) and CD19 (B cells) the discontinuation thresholds are 150 cells/µL and 50 cells/µL, respectively. Any subject who has CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below the discontinuation threshold as confirmed by a repeat test conducted within 1 week of the initial test will be discontinued from study drug.
b. Subjects with CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between the population-adjusted LLN and the discontinuation threshold will have lymphocyte subset counts performed on a weekly basis. (revised per Amendment 02) Subjects with a >33% reduction from baseline in CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts will also have lymphocyte subset counts performed on a weekly basis. During the early stages of the treatment period, where visits are conducted weekly (ie, Visits 4, 5, 6, and 7), lymphocyte subsets are already scheduled to be measured on a weekly basis and so additional visits or blood draws are not required. (revised per Amendment 02) For these subjects, the decision as to whether the subject remains on study drug or is to be discontinued from study drug will be based upon clinical judgment and will take into account any clinical presentation in addition to the lymphocyte subset counts. These subjects may continue with treatment if there is no clinical evidence of infection. They will be discontinued from study drug if they have infections of a moderate to severe intensity (eg, subjects whose infections are not localized, or are systemically unwell, or who require systemic anti-infective drug treatment).

**Table 1 Study Drug Actions for Lymphocyte Subset Absolute Counts**

| Lymphocyte subset absolute counts | Action | Decision to continue or discontinue |
|---|---|---|
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold | Retest within 1 week along with CBC with differentials | If retest performed within 1 week confirms lymphocyte subset counts below the discontinuation threshold, discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between population-adjusted LLN and discontinuation threshold or >33% reduction from baseline in CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts | Lymphocyte subset counts (and CBC with differentials) to be performed weekly until lymphocyte subset counts return to ≥ population-adjusted LLN or no more than 33% reduction from baseline | Decision will be based upon lymphocyte subset counts and clinical judgment |

LLN = lower limit of normal, CBC = complete blood count. (table revised per Amendment 02)

c. Subjects with clinical evidence of infection will have their CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts measured. Blood and other biological samples will also be collected for investigations of infective pathogens (eg, serological tests, quantitative polymerase chain reaction, microscopy, and culture) where appropriate. In subjects with infection, if any of their absolute cell counts meets the discontinuation thresholds, study drug will be discontinued. All subjects with severe infections will be discontinued from study drug. All subjects with herpes zoster (shingles) or ocular herpes infections will be discontinued from study drug, regardless of severity of presentation. Subjects with mild or moderate infection may continue treatment with study drug unless otherwise clinically indicated or otherwise specified below. Specifically, when any of the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are between the population-adjusted LLN and the discontinuation thresholds or have shown >33% reduction from baseline, subjects with infections of moderate intensity will be discontinued from study drug (eg, subjects whose infections are not localized, or subjects who are systemically unwell, or who require systemic anti-infective drug treatment). All subjects with infection who are discontinued from study drug will be followed for a period of 12 weeks or until the infection resolves/ stabilizes or until the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts have returned to greater than population-adjusted LLN (whichever comes latest). (revised per Amendment 02)

**Table 2 Study Drug Actions for Lymphocyte Subset Absolute Counts and Infection**

| Criterion | Severity of Infection | | | |
|---|---|---|---|---|
| | None | Mild | Moderate | Severe |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold | If confirmed with repeat testing within 1 week, then discontinue study drug. | Discontinue study drug | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between population-adjusted LLN and discontinuation threshold or >33% reduction from baseline in CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts always > population-adjusted LLN and no reduction from baseline >33% | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated | May continue treatment with study drug unless discontinuation is clinically indicated (See (e) for exception) | Discontinue study drug |

LLN = lower limit of normal. Table revised per Amendment 02

d. A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (see (e) for exception), will be discontinued from study drug and a dermatological consult will be requested regardless of whether the rash is considered drug-related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatological consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

e. Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

f. Development of any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. If discontinued from study drug, subjects will undergo an ED Visit within 7 days after discontinuation and will attend the Follow-Up Visits 4 and 12 weeks after the last dose of study drug. They will also undertake an Unscheduled Visit (with MRI) at approximately 4 weeks after the visit at which such MRI features were first identified. An MRI will also be performed at approximately the time of the second Follow-Up Visit (Visit 20). Additional visits for safety may be arranged if clinically indicated in the opinion of the investigator, including after 12 weeks after the last dose of study drug. At any time during the treatment period, subjects who have asymptomatic, treatment-emergent microhemorrhages as detected by MRI, but none of the features which merit discontinuation of treatment (ie, vasogenic edema, macrohemorrhage, an area of

superficial siderosis, or a symptomatic treatment-emergent microhemorrhage) may continue with treatment. These subjects will have safety assessments (including MRI) at approximately 4 weeks after the visit at which such MRI features were found. They will also continue with the scheduled MRI scans. Additional unscheduled MRI scans may be arranged on an individual subject basis in discussion with the study medical monitor.

g. A postdose ECG with an average QTcF interval >500 msec from triplicate ECGs
h. A postdose ECG with a QTcF interval increase from baseline >60 msec and a QTcF interval >450 msec as demonstrated from triplicate ECGs
i. Any seizure (motor or non-motor)
j. Pregnancy

## 9.4 Treatments

### 9.4.1 Treatments Administered

For this study the test drug is E2609 and the control drug is placebo. All study drugs are to be administered orally, QD, with food.

Treatments to be administered in Stage A and Stage B are shown below and in Figure 1.

The 2 highest E2609 doses (15 and 50 mg) taken into Stage B, after the PK/PD and safety review from Stage A, will be used for the mild to moderate AD population in Stage B. (revised per Amendment 01)

- Stage A: 3 doses (5, 15, and 50 mg) of E2609 or placebo
- Stage B, MCI/Prodromal Cohort: 3 doses (5, 15, and 50 mg) of E2609 or placebo
- Stage B, Mild to Moderate AD Cohort: 2 doses (15 and 50 mg) of E2609 or placebo. (revised per Amendment 01)

Study treatment will begin on Day 1 (at the study site) following Randomization and will continue for approximately 78 weeks. Please refer to Table 7 and Section 9.5.1.4.1 for specific information on drug administration on days when PK sampling is to be performed.

Study drug doses will remain the same for each individual subject unless the interim PK/PD analysis determines that an entire dose level requires adjustment (Section 9.4.4). See Section 9.3.3 for safety-related discontinuation criteria of study drug. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

### 9.4.2 Identity of Investigational Product

E2609 tablets of 5-, 10-, and 25-mg dose strengths will be supplied. Placebo tablets of identical appearance will also be available. Each subject will receive 2 tablets, which combined will make up the required doses of E2609 5, 15, 50 mg, or placebo. The tablets

will be supplied by the Sponsor in labeled blister packs. The product release certificates for E2609 and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either E2609 or placebo, or both (see Section 9.4.2.3 for labeling details).

#### 9.4.2.1 Chemical Name and Formula of E2609

- Test drug code: E2609
- Generic name: not applicable
- Chemical name: International Union of Pure and Applied Chemistry
- *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

#### 9.4.2.2 Comparator Drug

Not applicable.

#### 9.4.2.3 Labeling for Study Drug

E2609 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier (ID)
- Lot number/batch number
- Storage conditions, expiration date if necessary

#### 9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data

acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

### 9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used for Stage A (all subjects), for Stage B MCI/Prodromal subjects and Stage B for mild to moderate AD subjects are described in Section 9.4.1. (revised per Amendment 01)

Randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized blister card identification numbers. At enrollment, the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 3), the IxRS will assign each subject a unique randomization number.

### 9.4.4 Selection of Doses in the Study

It is not known how the level of CSF or brain Aβ reduction is related to clinical efficacy. Therefore, in this study, doses will be selected such that at steady state, they will result in 25%, 50%, and 75% reduction in CSF Aβ levels from baseline to cover a broad range of PD effects.

In Study 007, the relative bioavailability of a tablet formulation of E2609 in the fed and the fasted states compared with the capsule formulation in the fasted state (used in Studies 001 and 002) was investigated. It was found that when the tablet form of E2609 (50 mg) was administered with food, the exposure (ie, AUC) of the parent drug E2609 was higher, with lower maximum observed concentrations and reduced exposure to the metabolites, compared with either formulation in the fasted state.

Based on the PK/PD modeling using data from healthy volunteer Studies 001, 002, and 007, doses of 5, 15, and 50 mg QD administered as the tablet formulation with food in this study should achieve CSF Aβ reduction from baseline of approximately 25%, 50%, and 75% at steady state, respectively (Table 3).

**Table 3 Predicted Steady State Plasma PK Parameters and CSF Amyloid β Reduction From Baseline**

| E2609 Tablet Daily Dose (mg) With Food | E2609 Plasma $C_{max,ss}$ (ng/ml) | E2609 Plasma $C_{ss,av}$ (ng/ml) | E2609 Plasma $AUC_{(0-24h)ss}$ (ng.h/ml) | % Reduction CSF BACE1 Activity | % Reduction CSF Aβ(1-x) |
|---|---|---|---|---|---|
| 5 | 6.2 | 3.3 | 80.3 | 16.2 | 33 |
| 15 | 18.6 | 10 | 240.9 | 36.6 | 56 |
| 50 | 62.1 | 33.5 | 803.0 | 65.7 | 79 |

Aβ(1-x) = amyloid beta monomer from amino acid 1 to x, $AUC_{(0-24h)ss}$ = area under the concentration x time curve at steady state from time zero to 24 hours, BACE1 = Beta-amyloid converting enzyme, CSF = cerebrospinal fluid, $C_{ss,av}$ = average steady-state concentration, $C_{max,ss}$ = maximum plasma concentration at steady state, PK = pharmacokinetics.

The PK/PD modeling described above, which was conducted using data obtained from healthy volunteers, has also been supported by modeling of data from subjects with an underlying AD pathology (Study 101). Furthermore, external data with another BACE1 inhibitor (MK-8931) showed a similar PD effect in AD patients as in healthy volunteers (Forman, et al., 2013). Therefore we are confident that the modeling of E2609 effects in healthy subjects will be applicable for both MCI/Prodromal and mild to moderate AD dementia patients. (revised per Amendment 01)

The exposure of the highest dose in this study (50 mg QD tablet administered with food) is less than that of the 100 mg QD dose (capsule administered fasted) in Study 002.

The 100 mg QD dose administered for 14 days in Study 002 was well tolerated with no clinically significant changes in laboratory parameters, vital signs, or ECG parameters. On Day 15, for the 100 mg QD cohort in Study 002, there was a reduction of CD4 lymphocyte counts compared with placebo (CD4 lymphocyte counts on E2609 decreased by 3.1% from baseline, whereas the placebo control showed an increase of 8.7%), but this decrease was less than that observed at doses of 200 mg (22.9% decrease) or 400 mg (17.3% decrease). No subjects had infections or drug rash while receiving E2609 100 mg QD or at lower doses in Study 002, whereas at 200 and 400 mg QD, 4 subjects had symptomatic orolabial HSV1 relapses and 2 subjects at the highest dose had drug rash. The highest dose for Study 202 of 50 mg QD (tablet administered with food) is therefore expected to have a similar or better safety profile compared with the 100 mg QD capsule (administered fasted) in Study 002. Specific exclusion criteria, blinded and unblinded safety monitoring procedures, and safety criteria for discontinuation from study drug are included in this study in order to mitigate any immunology-related risk with E2609, particularly in light of the progression from 14 days of dosing (Study 002) to 18 months of dosing in this study.

In Stage A, all subjects will be randomized to receive either placebo or E2609 at 5, 15, or 50 mg QD. In Stage B, subjects in the MCI/Prodromal cohort will continue to be randomized to receive either placebo or E2609 at 5, 15, or 50 mg QD. In Stage B, subjects in the Mild to Moderate AD cohort will be randomized to receive either placebo or E2609 at 15 or 50 mg QD, but not the 5-mg QD dose. The rationale for not including an E2609 5-mg QD dose in the dose regimens for Stage B subjects with mild to moderate AD is that more

advanced disease may require greater reduction in CSF Aβ levels for comparable effects. (revised per Amendment 01)

Interim analyses of the E2609 PK and PD profiles will be performed on subjects who have provided CSF samples at Baseline and after 4 weeks of study drug. These data will be used to evaluate the CSF PD effects of E2609 doses, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels. (revised per Amendments 01 and 02) The mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment for each dose of E2609 and its 90% confidence interval will be derived. In addition, exploratory PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data from Stage A and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline after 4 weeks of dosing. (revised per Amendment 02)

If dose adjustment is required for Stage B, a protocol amendment reflecting the new doses will be submitted.

### 9.4.5 Selection and Timing of Dose for Each Subject

E2609 is administered orally, QD, with food. Study treatment will begin on Day 1 following randomization and will continue for approximately 78 weeks.

### 9.4.6 Blinding

E2609 and placebo will be administered as tablets of identical appearance.

During the Randomization Phase and Follow-Up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and Eisai staff will be blinded to the treatment codes (double-blind).

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (ie, those who are trained and certified to perform the various cognitive assessments that are undertaken in this study). Furthermore, at the site, the notes and reports relating to safety assessments must be kept separate from the notes and reports relating to efficacy, particularly for the CDR. (revised per Amendment 01)

Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

The PK/PD interim analysis to evaluate the E2609 doses to be used for Stage B will be conducted by an independent group (revised per Amendment 02). Any changes to dose will be reflected in an amendment to the protocol and the Statistical Analysis Plan will detail how data will be handled in the primary analysis.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

At the conclusion of the study, all unused drug supplies are to be returned to the Eisai approved contract packaging vendor.

### 9.4.7 Prior and Concomitant Therapy

Medication (including over-the-counter medications) or therapy administered to the subject before the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2. Prohibited medications are presented in Listing 1, Listing 2, Listing 3, Listing 4, Listing 5, and Listing 6. Medications that are permitted with restrictions are listed in Listing 7, Listing 8, and Listing 9.

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit:

- Anticoagulants (eg, warfarin, digabatrin) are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization
- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization

Subjects taking AChEIs or memantine must meet the following criteria in order to be included in the primary analyses:

- On a stable dose for 12 weeks before the Baseline cognitive assessments at Visit 2

- Remain on a stable dose while on study

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for the primary analyses.

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety, and are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks.

### 9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period. CRAs will review treatment compliance during site visits and at the completion of the study.

### 9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number

- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the principal investigator including a copy of the principal investigator's current medical license (required for United States sites) or medical registration number on the curriculum vitae
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or

local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

## 9.5 Study Assessments

### 9.5.1 Assessments

#### 9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

#### 9.5.1.2 Baseline Assessments

Assessments to be made at Screening and Baseline and throughout the study are described in Section 9.5.1.3, Section 9.5.1.4, and Section 9.5.1.5.

##### 9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, current medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment due to AD. Subjects will be asked about history of TB, infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV Types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include onset, duration, relapse frequency, severity, and treatments. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The 15-item GDS and modified Hachinski ischemic scale will also be assessed at Screening as part of the exclusion criteria.

Physical examinations (complete or routine) will be performed as designated in Table 6. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, and skin, and a neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### 9.5.1.2.2 VIRAL TESTING

As specified in Table 6, blood will be collected for screening for Hepatitis B and Hepatitis C for determining eligibility, and at Baseline for viral characterization.

#### 9.5.1.2.3 B12 TESTING

Blood will also be collected for vitamin B12 levels as specified in Table 6.

#### 9.5.1.2.4 TB EXPOSURE TESTING

Blood will also be collected for testing for previous TB exposure, as specified in Table 6.

#### 9.5.1.2.5 URINE DRUG TESTING

Urine will be collected for drug screening as specified in Table 6.

### 9.5.1.3 Efficacy Assessments

#### 9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

The timing of psychometric assessments is shown in Table 6 and Table 7. These assessments should be administered in the morning (or, if not possible, consistently at the same time of day) and should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). At the Screening Visit, the recommended order of assessments is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. At the Baseline Visit, the assessments are to be conducted in the following order: MMSE, CDR, ADAS-cog$_{14}$, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). (revised per Amendment 02)

At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

**The Derived Alzheimer's Disease Composite Score:** The primary efficacy endpoint is the change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects.

The ADCOMS is derived from the ADAS-cog (4 items), the MMSE (2 items), and the CDR (all 6 items), described below. The ADCOMS is more sensitive to clinical progression compared with currently existing clinical batteries and requires smaller sample sizes for clinical studies in MCI/Prodromal AD or mild to moderate AD. (revised per Amendment 01) It also shows sensitivity to treatment effects with AChEIs. The ADCOMS assesses both cognitive and functional domains and can be offered as a single primary clinical endpoint. The ADCOMS has a range from 0 to 1.97.

**CogState Brief Battery:** The CBB is a computer-based battery comprising 4 cognitive tests:

1. Detection – a simple reaction time test where the subject presses a key when the card is turned face up from a pack of cards ("Has the card turned over"). Speed of response is the measure.
2. Identification – a simple choice reaction time test where the subject presses 1 of 2 keys when the card just turned face up is either a red card or a black card ("Is the card red"). Speed of response is the measure.
3. One Card Back – a simple working memory test where the subject presses 1 of 2 keys when the card turned face up is either the card seen in the immediately previous trial or not ("Is the previous card the same"). Accuracy of response is the measure.
4. One Card Learning – a visual learning and memory test where the subject presses 1 of 2 keys depending on whether the card just turned face up has been seen before or not in the task ("Have you seen this card before in this task"). Accuracy of response is the measure.

**ISLT:** The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 15 minutes, in which time the CBB is performed, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

**Mini Mental State Examination:** A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

**Clinical Dementia Rating:** The CDR assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

**Alzheimer's Disease Assessment Scale - cognitive subscale:** Discussed in Section 9.2.4.

**Functional Assessment Questionnaire:** Either a caregiver or informant or the subject provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

#### 9.5.1.3.2 VOLUMETRIC MRI

Volumetric MRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the Alzheimer's Disease Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume

provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

Volumetric MRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. Volumetric MRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. Volumetric MRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 6 and Table 7, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

For subjects who consent to CSF sample collection, CSF samples will be collected by LP (gravity drip method) at the timepoints specified in Table 6 and Table 7 (revised per Amendment 02). The CSF sample taken at the Baseline Visit will only be performed after subjects consent to CSF sample collection, and after confirmation of an amyloid positive PET scan (revised per Amendment 02). See Section 9.5.1.4.2 for further details.

### 9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

#### 9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of E2609. For subjects who consent to CSF sample collection, CSF samples will be collected for the determination of E2609 concentrations. (revised per Amendment 02) Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with E2609.

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 6 and Table 7. Two PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visits 5, 11, 14, and 16, and 4 to 8 hours postdose at Visit 7 and Visit 18 (or at the ED Visit). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug with food at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or at the ED Visit) the PK blood sample should be collected shortly before or shortly after

completing the LP. (revised per Amendment 01) Although the PK sampling procedures at the ED visit should follow those of Visit 18, in the event that study drug has already been discontinued prior to the ED visit, then no dosing will be conducted. However, a PK sample at trough (before LP) will be collected, followed by LP at approximately the same time as previous visits. A second PK blood sample will be collected as close as possible in time to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

#### 9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

**Biomarkers**

Subjects who consent to CSF sample collection will be encouraged to stay at the site after completion of LP for medical observation (revised per Amendment 02). At Baseline, a CSF sample will be collected by LP (gravity drip method) after fasting (preferred), or at least 2 hours after the most recent meal. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. At visits where cognitive tests are also performed, if the tests are to be performed on the same day, the LP must be performed after the cognitive tests have been completed and the subjects should rest and drink some fluid to hydrate before the LP. (revised per Amendment 01) The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. The CSF sample will be used for PD assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), t-tau, p-tau, and BACE. The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses (eg, miRNA). Aβ(1-x) in both CSF and plasma will be measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and post-screening analysis of CSF Aβ(1-42), t-tau, and p tau will be performed using ELISAs. BACE1 levels will be measured using internally developed fluorescence resonance energy transfer and ELISA based assay(s). Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

The blood sample collected for PD analyses at Baseline should be collected on the same day shortly before or shortly after completing the LP at Baseline. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

At the Baseline Visit, blood samples will be collected and stored for determination of prior exposure to any suspected infective agents in the event that the subject develops treatment-emergent AEs that warrant further investigation (eg, treatment-emergent infection). For subjects who consent to CSF sample collection, CSF samples from the Baseline Visit will also be stored for the same purpose. (revised per Amendment 02) Testing may include, but

not be limited to, serological tests, viral titer by quantitative polymerase chain reaction, or human leukocyte antigen genotyping.

Blood samples will be collected for PD assessments as specified in Table 6 and Table 7. See Section 9.5.1.4.2 for further details.

For all subjects, baseline and on-study blood samples, DNA samples, and any CSF samples collected from subjects who consent to CSF collection will be stored for up to 15 years. (revised per Amendment 02)

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

**Pharmacogenomics**

A blood sample will be obtained at Baseline and will be used to determine the *ApoE* genotype (homozygous or heterozygous E4 versus non-E4) and the *NAT2* phenotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response, safety, or PK of E2609. Details of which genotype / phenotype data will be applied to the analyses of efficacy, safety or PK will be discussed in the Statistical Analysis Plan.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

**Amyloid PET**

An amyloid PET scan will be performed at Screening to confirm deposition of amyloid in the brain. An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02) Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects with Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses) and will only be conducted until acceptable 18-month PET scans have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used (Table 6). (revised per Amendment 02) PET scanning will be performed with a locally approved Aβ imaging agent (eg, Amyvid). Descriptions and detailed instructions for all imaging can be found in the imaging manual.

Amyloid PET imaging is an exploratory measure of the potential disease-modifying effects of E2609.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, lymphocyte subsets, Igs, and urine values; periodic measurement of vital signs and ECGs; performance of physical and neurological examinations; centralized dermatological assessments; the C-SSRS; and safety MRIs as detailed in Table 6 and Table 7 will also be conducted. Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and posttreatment for exploratory immunomodulatory and immune-based analyses.

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (see Section 9.4.6). (revised per Amendment 01)

##### 9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E2609.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: It is not necessary to report every sign or symptom as a separate AE if the overall disease [diagnosis] is being reported as an AE.)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, discontinuation of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 20, as shown in Table 7). For subjects who discontinue early from study drug but undertake further efficacy assessments, AEs will only be collected for 3 months after the last dose of study drug, ie, through to the second follow-up visit (Visit 20). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF. SAEs will be

collected for 3 months after the last dose of study drug, ie, through to the second follow-up visit (Visit 20). For subjects who discontinue early from study drug but continue with further efficacy assessments, SAEs will be solicited only for 3 months after the last dose of study drug, i.e. up to the 2nd follow up visit (Visit 20). However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the ADCOMS, ADAS-cog$_{14}$, MMSE, and CBB (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 4.

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis
- Dissociative state

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be

exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.11 for a description of the C-SSRS).

The following adverse events will require the collection of information sufficient to provide a detailed description of the event, treatment and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection; any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a "yes" answer to Type 4 or 5 suicidal ideation, or a "yes" response to any suicidal behavior on the C-SSRS.

All AEs must be followed through the second follow-up visit (Visit 20), or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

**Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.**

### Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

| | |
|---|---|
| Mild | Discomfort noticed, but no disruption of normal daily activity |
| Moderate | Discomfort sufficient to reduce or affect normal daily activity |
| Severe | Incapacitating, with inability to work or to perform normal daily activity |

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

### Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

*Classification of Causality*

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

#### 9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reportable using the criteria of important medical event if the event does not meet other serious criteria: new onset seizures, ocular herpes.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the eCRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

#### 9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 4. Subjects should be in a seated or supine position during blood collection. Table 6 and Table 7 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

See Section 9.3.3 for safety criteria for discontinuation from study drug related to absolute counts of CD4, CD8, and B lymphocytes, and for lymphocyte subset counts.

**Table 4 Clinical Laboratory Tests**

| Category | Parameters |
|---|---|
| **Hematology** | Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils).<br><br>PT, PTT, and INR (Screening and Baseline only) (revised per Amendment 02) |
| **Chemistry** | |
| **Electrolytes** | Bicarbonate, calcium, chloride, phosphate, potassium, sodium |
| **Liver function tests** | Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin |
| **Renal function tests** | Blood urea/blood urea nitrogen, creatinine |
| **Other** | Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid |
| **Urinalysis** | Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells |
| **Other** | Lymphocyte subset analyses (see Table 5). Regulatory T cells will be measured using CD4, CD25, and FoxP3 intracellular marker.<br>PBMCs (revised per Amendment 02)<br>Ig analyses (IgG, IgA, and IgM).<br>Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]).<br>Viral characterization (including HSV1, HSV2 and CMV, etc)<br>Serum pregnancy test (females of child bearing potential only)<br>Tuberculosis Interferon Gamma Release Assays<br>Tests for thyroid function (thyroid stimulating hormone, free triidothyronine and free thyroxine) and vitamin B12<br>Blood sample for storage for subsequent testing of immune status |

## Table 4 Clinical Laboratory Tests

| Category | Parameters |
|---|---|
| | Cerebrospinal fluid sampling |

Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials, must also be repeated. (revised per Amendment 02)

CMV = cytomegalovirus, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV = herpes simplex virus, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PT = prothrombin time, PTT = partial thromboplastin time.

The 8 different surface markers (CD3, CD4, CD8, CD45, CD19, CD16, CD56, and CD14) and total lymphocyte counts will be measured in order to provide the lymphocyte subset data as shown in Table 5. In addition, Regulatory T cells will be measured using CD4, CD25, and FoxP3 intracellular marker. Current sponsor data supports the literature showing there is an age-related decline in lymphocyte subsets (see Appendix 5). These data have been used to revise the LLNs for CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts to the population-adjusted LLNs of 396, 157, and 74 cells/µL, respectively) (revised per Amendment 02).

## Table 5 Lymphocyte Subtyping

| Cell Type | Cell Surface Markers |
|---|---|
| T lymphocytes | CD3 |
| T helper cells | CD3+, CD4 |
| Cytotoxic T cells | CD3+, CD8 |
| Mature B cells | CD3-, CD19 |
| Natural killer cells | CD3-, CD16, CD56 |
| Macrophages | CD14 |

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the case report form [CRF] Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

#### 9.5.1.5.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [bpm], respiratory rate [per minute], body temperature [in centigrade], and weight [kg]) will be obtained at the visits designated in Table 6 and Table 7 by a validated method. Measurements of sitting BP and heart rate will be obtained. All BP measurements should be performed on the same arm, preferably by the same person.

#### 9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination will be performed at Screening as described in Section 9.5.1.2.1. At Baseline and during the Randomization Phase, routine physical examinations will take place as shown in Table 7. These examinations will include the cardiovascular system, respiratory system, and neurological system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 6 and Table 7. Twelve-lead standard ECGs will be recorded in triplicate (1 minute apart) after subjects have been resting in the supine position for at least 5 minutes.

On any study day when ECG, vital signs, and blood samples are taken, these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.7 SAFETY MRI

Safety brain MRI assessments will be performed at the times shown in Table 6 and Table 7. Additional safety MRI scans can be performed at unscheduled visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Safety MRIs will be acquired using a standardized procedure that will include fluid-attenuated inversion recovery (FLAIR), gradient-echo, T1, and diffusion-weighted sequences to determine the presence of focal lesions including, but not limited to, evidence for ischemic and hemorrhagic stroke, subdural hematoma, neoplasm, arteriovenous malformation, micro and macrohemorrhages, superficial siderosis, lacunar infarcts, white matter abnormalities, and vasogenic edema. The imaging sequence for the Screening/safety MRI will include: T2 weighted anatomic MRI to rule out major white matter changes, cerebral infarction or other structural lesions, and a high-resolution 3D T1-weighted scan with isotropic voxels with volumes of 1 $mm^3$ or less. In addition, both FLAIR for the detection of vasogenic edema and T2* Gradient Recall Echo for the detection of microhemorrhages will be acquired. The 3D dataset will be reconstructed in transverse slices in Digital Imaging and Communications in Medicine format. The results of this MRI

assessment will also be used as the Baseline Period MRI, against which changes after drug administration will be compared. Further details of the MRI protocol can be found in the Imaging Acquisition Guideline. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, and 18 and at the second Follow-Up Visit (Visit 20). In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

At any time during the treatment period, subjects will be discontinued from study drug if they develop any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. All of these features must be reported as study specific AEs (or AEs of special interest). These subjects will undergo an ED Visit within 7 days after discontinuation and Follow-Up Visits at 4 weeks and 12 weeks after the last dose of treatment. Subjects will also undertake an Unscheduled Visit (with MRI) at approximately 30 days after the visit at which such MRI features were first identified. Additional visits may be arranged if clinically indicated in the opinion of the investigator, and may occur later than 12 weeks after the final dose of study drug.

#### 9.5.1.5.8 DERMATOLOGICAL ASSESSMENT

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at the times shown in Table 6 and Table 7. These assessments will specifically include evaluation of any areas of depigmentation or any rash.

In addition, subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregiver or informants will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or infection, and the investigator will be required to review such AEs as soon as possible and consider an unscheduled physical and dermatological evaluation. Detailed characteristics of any skin rashes will be captured in the clinical database. Physical examination may be undertaken where indicated. Treatment-emergent abnormal dermatological findings should be reported as AEs.

#### 9.5.1.5.9 NEUROLOGICAL EXAMINATION

Neurological examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations as shown in Table 6 and Table 7. Details of these examinations will be captured in an eCRF. The neurological examinations will monitor for new symptoms and signs which will then alert the investigator to consider new CNS pathology (especially slowly-evolving neurological conditions that may not lead to prominent symptoms). Examples of neurological signs that may indicate new CNS

pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. In such a situation, the investigator should consider (but not limited to) demyelination in the differential diagnoses, and should discuss with the sponsor's medical monitor further investigations or treatment, which will be decided case by case. Neurological examinations will also include the assessment of cranial nerve function, especially the olfactory nerve. Treatment-emergent abnormal neurological findings should be reported as AEs.

#### 9.5.1.5.10 PREGNANCY TEST

At Screening, females of childbearing potential will have a serum pregnancy test. At Baseline and during the Treatment Period, urine samples will be obtained from females of childbearing potential for pregnancy tests (see Table 7).

#### 9.5.1.5.11 COLUMBIA SUICIDE SEVERITY RATING SCALE

An assessment of suicidal ideation and behavior using the C-SSRS will be performed at the designed time points in Table 6 and Table 7. A "yes" answer to Type 4 or 5 suicidal ideation or a "yes" response to any suicidal behavior queries will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

#### 9.5.1.5.12 BIOMARKER SAMPLES

As noted in Section 9.5.1.4.2, CSF (for subjects who consent to CSF sample collection), blood, and DNA samples will be collected and may be used for exploratory biomarker analyses, as well as tested in the event that a subject develops AEs that warrant further investigation. (revised per Amendment 02)

#### 9.5.1.5.13 OPHTHALMIC EXAMINATIONS

An ophthalmic examination will be conducted at Baseline (unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available). An additional examination will be conducted, if the subject experiences visual disturbances during the course of the study or is medically indicated. The ophthalmic examinations should include fundoscopy to look at the optic disc, macula and the rest of the retina, as well as an assessment of visual acuity and visual fields.

### 9.5.2 Schedule of Procedures/Assessments

#### 9.5.2.1 Schedule of Procedures/Assessments

Table 6 presents the Schedule of Procedures/Assessments for the Prerandomization Phase. Screening assessments will be organized into 4 tiers (see below and Figure 2).

Table 7 presents the Schedule of Procedures/Assessments for the Randomization Phase.

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

| Phase | Prerandomization | |
|---|---|---|
| Period | Screening | Baseline |
| Visit | 1 | 2 |
| **Procedures/ Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)** | | |
| Informed consent (subject and caregiver or informant) | X (Tier 1) | |
| Subject informed consent for CSF sample collection (voluntary) | X | X |
| Demographics | X (Tier 1) | |
| Medical history[a] | X (Tier 1) | |
| Prior / concomitant medications[b] | X (Tier 1) | X |
| Vital signs including weight[c] | X (Tier 1) | X |
| Height | X (Tier 1) | |
| Complete physical examination | X (Tier 1) | |
| Routine physical examination | | X |
| CBB and ISLT[d] | X (Tier 1) | X |
| MMSE[d] | X (Tier 1) | X |
| CDR[d] | X (Tier 1) | X |
| FAQ[d] | X (Tier 1) | X |
| ADAS-cog14[d] | | X |
| 15-item Geriatric Depression Scale | X (Tier 2) | |
| Modified Hachinski ischemic scale | X (Tier 2) | |
| C-SSRS | X (Tier 2) | X |
| 12-lead ECG[e] | X (Tier 2) | X |
| Blood and urine for clinical laboratory tests[f] | X (Tier 2) | X |
| Blood for lymphocyte subset analyses[g] | X (Tier 2) | X |
| Blood for Ig analyses[h] | X (Tier 2) | X |
| Blood for viral screen[i] | X (Tier 2) | |
| Blood for thyroid function tests[j] | X (Tier 2) | |
| Blood for vitamin B12 test | X (Tier 2) | |
| Test for previous TB exposure | X (Tier 2) | |
| Urine drug screen | X (Tier 2) | |
| Serum pregnancy test (females of childbearing potential only) | X (Tier 2) | |
| Urine pregnancy test (females of childbearing potential only) | | X |
| Safety and Volumetric MRI[k] | X (Tier 3) | |
| Amyloid PET scan[l] | X (Tier 4) | |
| Inclusion and Exclusion criteria | X (All tiers) | X |
| Adverse events | X (All tiers) | X |
| CSF sampling for PK, PD and storage[m] | | X |
| Blood sample for PK assessments[n] | | X |
| Blood sample for PD and exploratory biomarker assessments[o] | | X |
| Blood sample for pharmacogenomics | | X |
| Blood sample for storage for immune status[p] | | X |
| Blood sample for PBMC isolation | | X |
| Blood sample for viral characterization[q] | | X |
| Centralized dermatological assessment via photography[r] | | X |
| Neurological examinations[s] | | X |
| Ophthalmic assessment[t] | | X |

Table revised per Amendment 02

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

AChEI = acetylcholinesterase inhibitor, AD = Alzheimer's disease, ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CDR = Clinical Dementia Rating, CMV = cytomegalovirus, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), Ig = immunoglobulin, INR = International Normalized Ratio, ISLT = International Shopping List Task (immediate and delayed recall), LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetics, PET = positron emission tomography, PT = prothrombin time, PTT = partial thromboplastin time, TB = tuberculosis.

Note: Screening assessments/procedures have been organized into 4 distinct tiers. All assessments and procedures in each tier should be completed (see Figure 2), and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures, as long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. Similarly, all screening assessments and procedures must be completed, and eligibility to continue in the study confirmed, before any baseline assessments and procedures commence. Adverse events and eligibility against inclusion and exclusion criteria must be assessed at each stage within the Screening Visit and at the Baseline Visit. (revised per Amendment 01)

Note: All screening and baseline assessments are to be completed within 50 days, plus an additional window of up to 30 days if required (revised per Amendment 02). The interval between availability of the results of the last screening assessment (PET scan) and the first baseline (Visit 2) assessments should be as short as possible and ideally should not exceed 7 days. Visit 3 (Randomization) (see Table 7) should occur no more than 10 days after completion of the Baseline visit (Visit 2) and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion No.20 into account (revised per Amendment 02). Thus, the total Prerandomization Phase may be up to 60 days, plus an additional window of up to 30 days if required (revised per Amendment 02).

a: To include: mild cognitive impairment and AD history; history of TB, vaccination history against and infections due to varicella zoster virus (chickenpox and herpes zoster or shingles); infections due to HSV1 (orolabial herpes or cold sores) and 2 (genital herpes). Medical history of infections to include: onset, duration, relapse frequency, severity, and treatments. For any active infection within the last 4 weeks prior to randomization, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests (eg, MMSE, CDR) and safety laboratory tests conducted at Visit 2 must be repeated. (revised per Amendment 02)

b: Prior and concomitant medications include AChEIs and memantine, and other medications for cognitive decline.

c: Weight, respiratory rate, body temperature, and sitting blood pressure and heart rate will be obtained.

d: To be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). At the Screening Visit, the recommended order of assessments is: MMSE, ISLT (immediate recall), CBB, ISLT (delayed recall), CBB (repeat CBB for additional practice), CDR, and FAQ. The CBB may be repeated multiple times if required for the subject to pass completion and integrity criteria. At the Baseline Visit, the assessments are to be conducted in the following order: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). (revised per Amendment 02) At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

e: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

f: Clinical laboratory tests consist of hematology (including PT, PTT, and INR), clinical chemistry, and urinalysis.

g: Lymphocyte subsets to be measured include CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cells), CD16/CD56 (natural killer cells) and CD14 (macrophages). Regulatory T cells will also be measured (CD4, CD25, FoxP3). Viability staining may also be employed. Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a CBC with differentials, must also be repeated. (revised per Amendment 02)

h: Igs to be analyzed include IgG, IgA and IgM.

i: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

j: Thyroid function tests include thyroid stimulating hormone, free triidothyronine and free thyroxine.

k: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images. MRI will be read by an approved central reader. Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

assessments in the same imaging session. (revised per Amendment 01)

l: PET scanning will be performed with a locally approved β-amyloid imaging agent, eg, Amyvid if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. The PET image will be centrally read for the purpose of determining eligibility for inclusion into the study. An historical amyloid positive PET scan may be used if conducted within the previous 12 months and provided that the scan and result are considered acceptable by the central PET reading group. (revised per Amendment 02)

m: For subjects who consent to CSF sample collection: CSF will be collected by LP after fasting (preferred), or at least 2 hours after the most recent meal. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 and Visit 18) can be performed at a similar time of day (±1 hour) for each individual subject. If the LP and cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. The CSF sample will be used for PK and PD assessments. A CSF sample will also be stored for testing in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection). (revised per Amendments 01 and 02)

n: The PK blood sample should be collected on the same day shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

o: The PD and exploratory biomarker blood sample should be collected shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

p: A blood sample will be collected at Baseline and stored. This sample may be used for exploratory biomarkers associated with study drug or disease, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

q: Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

r: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. See Section 9.5.1.5.8 for further details.

s: To be performed by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations. Section 9.5.1.5.9 details what is included in the neurological examination.

t: An ophthalmic examination will be conducted at Visit 2 unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available. The ophthalmic examination should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields.

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| Phase | Randomization | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Period | Treatment | | | | | | | | | | | | | | | | | Follow-Up | | |
| Visit[a] | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | ED[b] | 19[c] | 20[c] | UNS Visit[d] |
| Day | 1 | 8 | 15 | 22 | 29 | 43 | 57 | 71 | 85 | 113 | 141 | 183 | 274 | 365 | 456 | 547 | | 575 | 631 | |
| Week | 1 | 2 | 3 | 4 | 5 | 7 | 9 | 11 | 13 | 17 | 21 | 27 | 40 | 53 | 66 | 79 | | 83 | 91 | |
| Weeks elapsed since first dose | 0 | 1 | 2 | 3 | 4 | 6 | 8 | 10 | 12 | 16 | 20 | 26 | 39 | 52 | 65 | 78 | | 82 | 90 | |
| Nominal months elapsed since first dose | 0 | | | | 1 | | 2 | | 3 | 4 | 5 | 6 | 9 | 12 | 15 | 18 | | 19 | 21 | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | |
| Routine physical examination | X | | | | X | | X | | X | | | X | X | X | X | X | X | X | X[e] | X |
| Inclusion and Exclusion criteria | X | | | | | | | | | | | | | | | | | | | |
| Vital signs[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[e] | X |
| Respiratory rate | | | | | X | | X | | X | X | X | X | X | X | X | X | X | X | X[e] | X |
| Weight | | | | | | | | | X | | | X | X | X | X | X | X | | X | X |
| Centralized dermatological assessment via photography[g] | | | | | | | | | X | | | X | X | X | X | X | X | | X | X |
| Neurological examination[h] | | | | | | | | | | | | X | | X | | X | X | X | X | X |
| Ophthalmic examination[i] | | | | | | | | | | | | | | | | | | | | X |
| Concomitant medications[j] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG[k] | | | X | | X | | X | | X | | | X | | X | | X | X | X | X[e] | X |
| Clinical biochemistry and urinalysis | | | X | | X | | X | | X | | | X | X | X | X | X | X | X | X | X |
| Complete blood count | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood samples for lymphocyte subset analyses[l] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood samples for Igs[m] | | | | | X | | X | | X | | | X | | X | | X | X | X | X | X |
| Blood samples for isolation of PBMCs | | | X | | | | | | X | | | | | | | | | | X | |
| Urine pregnancy test (females of CBP only) | X[n] | | | | | | | | X | | | X | X | X | X | X | X | X | | X |
| Blood sample for storage for immune status[o] | | | | | X | | | | X | | | X | | X | | X | X | X | X | X |
| CBB and ISLT[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| MMSE[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| CDR[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| ADAS-cog$_{14}$[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |

**Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)**

| **Phase** | **Randomization** | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | | | | | **Follow-Up** | | |
| **Visit**[a] | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **ED**[b] | **19**[c] | **20**[c] | |
| **Day** | **1** | **8** | **15** | **22** | **29** | **43** | **57** | **71** | **85** | **113** | **141** | **183** | **274** | **365** | **456** | **547** | | **575** | **631** | **UNS Visit**[d] |
| **Week** | **1** | **2** | **3** | **4** | **5** | **7** | **9** | **11** | **13** | **17** | **21** | **27** | **40** | **53** | **66** | **79** | | **83** | **91** | |
| **Weeks elapsed since first dose** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **10** | **12** | **16** | **20** | **26** | **39** | **52** | **65** | **78** | | **82** | **90** | |
| **Nominal months elapsed since first dose** | **0** | | | | **1** | | **2** | | **3** | **4** | **5** | **6** | **9** | **12** | **15** | **18** | | **19** | **21** | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | |
| FAQ[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| C-SSRS | | | | | X | | X | | X | | | X | X | X | X | X | X | X | X[e] | X |
| Safety and Volumetric MRI[q] | | | | | | | | | | | | X | | X | | X | X | | X | X |
| Amyloid PET[r] | | | | | | | | | | | | | | | | X | X | | | |
| Telephone contact[s] | | | X | | X | | | | X | | | X | | X | | X | X | | | X |
| Blood samples for PK[t] | | | X | | X | | | | X | | | X | | X | | X | X | | | X |
| Blood samples for PD and exploratory biomarkers[u] | | | X | | X | | | | X | | | X | | X | | X | X | X | X | |
| CSF sampling for PK and PD[v] | | | | | X | | | | | | | | | | | X | X | | | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Sleep/dream questionnaire[w] | | | | | | | | | | | | | | | | | | | | X |
| Randomization | X | | | | | | | | | | | | | | | | | | | |
| Dispense study drug[x] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |

**Notes for Table 7**

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating scale, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), Ig = immunoglobulin, ISLT = International Shopping List Task, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, UNS = unscheduled.

a: Visit 3 should be conducted no more than 10 days after completion of the Baseline visit (Visit 2) assessments and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion #20 into account. (revised per Amendment 02) A window of ±3 days will be permitted for Visit 4 to 14 inclusive. A window of ±10 days will be permitted for Visit 15 to 18 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since first dose" at subsequent visits.

b: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 19 and Visit 20, respectively). Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie. at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB, and ISLT) will be conducted. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) after the Early Discontinuation Visit or within ± 8 days of either of the Follow-Up Visits (Visit 19 and Visit 20). Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

c: All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 19 and Visit 20 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up period.

d: Unscheduled visits may be conducted at any time that safety or safety MRI data indicate per protocol or as clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

e: Only if clinically significant abnormalities are found at Visit 19 and the investigator considers it necessary to repeat at Visit 20. Clinical biochemistry, urinalysis, CBC, lymphocyte subsets and Igs should always be performed at Visit 20, regardless of clinical significance at Visit 19. (revised per Amendment 02)

f: Measurements of body temperature and sitting blood pressure and heart rate will be obtained.

g: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. Additional UNS dermatological assessments should be conducted in response to any dermatological AEs of concern (eg, depigmentation, rash, herpetic lesion).

h: Examples of neurological signs that may indicate new central nervous system pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

i: If the subject experiences visual disturbances during the course of the study, the subject will be referred to a specialist for a further ophthalmic examination, which should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields

j: Please refer to Section 9.4.7, which details prohibited and permitted medications in the study and associated timeframes.

k: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

l: Lymphocyte subsets to be measured include CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [NK cells] and CD14 [macrophages]) and total

lymphocytes. Regulatory T cells will also be measured (CD4, CD25, and FoxP3). Viability staining may also be employed. Whenever unscheduled lymphocyte subset tests are performed or whenever scheduled lymphocyte subsets are repeated, a Complete Blood Count, with differentials, must also be performed. (revised per Amendment 02)

m: Igs to be analyzed include IgG, IgA, and IgM.

n: An additional assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

o: Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

p: These assessments are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The order of assessments will be: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). At visits where the CDR or FAQ are conducted, the investigator will determine whether the informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

q: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images in MRI will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, and 18 and 20. In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A volumetric MRI sequence will be collected in all subjects immediately following all safety MRI assessments. (revised per Amendment 01)

r: PET scanning will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks. A PET scan will only be performed at Visit 18 or ED if the subject has a valid Screening PET scan for the purposes of longitudinal analyses; subjects who were determined to be eligible for the study on the basis of an historical PET scan will not have a PET scan performed at Visit 18 or ED (revised per Amendment 02)

s: Site staff will contact the subject or the caregiver or informant the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the caregiver or informant, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

t: Two plasma PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visit 5, Visit 11, Visit 14 and Visit 16 and 4 to 8 hours postdose at Visit 7 and Visit 18 (or ED). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or ED) the PK blood sample should be collected shortly before or shortly after completing the LP. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected, followed by LP at approximately the same time as at previous visits. A second PK blood sample will be collected as close as possible to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

u: PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day. At Visits 5, 11, 14, and 16 the PD blood samples should be collected predose.

v: For subjects who consent to CSF sample collection: All visits at which CSF samples are scheduled to be taken also include blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Baseline LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If the LP and the cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the

CSF sample will still be collected unless it was already collected within the past 3 months. (revised per Amendments 01and 02)

w: Subjects reporting adverse events relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

x: The first dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time as determined by the PI or Safety Physician for postdose medical observation. (revised per Amendment 02)

#### 9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 6 and Table 7 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 4 tiers (see Table 6, Section 9.1.1.1, and Figure 2.

See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 8 presents the number of blood and CSF samples, and the total volume of blood and CSF that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety.

**Table 8 Summary of Blood and CSF Sample Volumes**

| Assessment | Total number of collection time points | Number of time points x volume per collection (mL whole blood or CSF) | | Total volume (mL whole blood or CSF) |
|---|---|---|---|---|
| | | Screening and Baseline Periods | Treatment and Follow-Up Periods | |
| **Blood** | | | | |
| Chemistry | 12 | 2 x 2 mL | 10 x 2 mL | 24 mL |
| Hematology | 18 | 2 x 5 mL | 16 x 5 mL | 90 mL |
| Lymphocyte subset analyses | 18 | 2 x 4 mL | 16 x 4 mL | 72 mL |
| PBMC | 4 | 1 x 16 mL | 3 x 16 mL | 64 mL |
| IgA, IgM, IgG | 9 | 2 x 2 mL | 7 x 2 mL | 18 mL |
| PT, PTT for INR | 2 | 2 x 3 mL | None | 6 mL |
| Thyroid function tests (thyroid stimulating hormone, free triidothyronine and free thyroxine) | 1 | 1 x 3 mL | None | 3 mL |
| Viral screen (Hepatitis B and C) | 1 | 1 x 4 mL | None | 4 mL |
| Viral characterization | 1 | 1 x 4 mL | None | 4 mL |
| Vitamin B12 | 1 | 1 x 2 mL | None | 2 mL |
| Serum pregnancy test | 1 | 1 x 2 mL | None | 2 mL |
| Tuberculosis (interferon-gamma release assays) | 1 | 1 x 3 mL | None | 3 mL |
| Sample for immune status | 8 | 1 x 4 mL | 7 x 4 mL | 32 mL |
| PD sample | 9 | 1 x 4 mL | 8 x 4 mL | 36 mL |
| PK analysis | 7 | 1 x 3 mL | 6 x 6 mL | 39 mL |
| Pharmacogenetic sample | 1 | 1 x 3 mL | None | 3 mL |
| All blood samples, total volume whole blood collected | | 80 mL | 322 mL | 402 mL |
| **CSF (For subjects who consent to CSF sample collection) (revised per Amendment 02)** | | | | |
| PD and PK samples | 3 | 1 x 12 mL | 2 x 12 mL | 36 mL |

CSF = cerebrospinal fluid, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetic, PT = prothrombin time, PTT = partial thromboplastin time.

### 9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include vital signs, clinical laboratory assessments, physical examinations, ECG measurements, and reports of AEs. MRI will be used to detect vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage and is a standard evaluation to ensure subject safety. The C-SSRS has been endorsed by the FDA as a measure of potential suicidality (Guidance for Industry Suicidality).

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, in addition to mitigating clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. Details are provided in Section 9.2.6.

### 9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

#### 9.5.4.1 Reporting of Serious Adverse Events

**All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.**

SAEs, regardless of causality assessment, must be collected up to 3 months after the last dose of study drug, ie, through to the second follow-up visit (Visit 20). In subjects who discontinue study drug early, but continue with efficacy assessments, SAEs only need to be solicited up to 3 months after the last dose of study drug. However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

**For urgent safety issues**, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

#### 9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must discontinue study treatment.

#### 9.5.4.3 Reporting of Events Associated with Special Situations

##### 9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

| | |
|---|---|
| Overdose | Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose |
| Misuse | Intentional and inappropriate use of study drug not in accordance with the protocol |
| Abuse | Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects |
| Medication error | Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject |

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

#### 9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2) should always be considered serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

### 9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

### 9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

#### 9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

### 9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue study drug or withdraw from the study at any time for any reason. All subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 19 and Visit 20, respectively) (see Section 9.1.2.3). See Table 7 for full details of the assessments to be performed at these visits. Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie, at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog14, FAQ, CBB and ISLT) will be conducted. Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above. Subjects who discontinue study drug early (as opposed to subjects whose dosing with study drug is temporarily suspended under Medical Monitor guidance) will not be permitted to restart study drug.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and will provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who withdraw prematurely from the study will be withdrawn for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for withdrawal from the study. Study disposition information will be collected on the Subject Disposition eCRF.

A subject removed from the study for any reason may not be replaced.

### 9.5.6 Abuse or Diversion of Study Drug

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Potential Abuse-related Medication Handling Event eCRF.

### 9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

## 9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

### 9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

### 9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy assessments performed in this study.

## 9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, except for the Bayesian methods on the primary endpoint.

### 9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the statistical analysis plan, which will be finalized before the first interim efficacy analysis.

#### 9.7.1.1 Study Endpoints

See Section 9.2.3 for a discussion of the rationale for the selection and clinical relevance of the primary study endpoint. Further information on the derived ADCOMS is described in Section 9.5.1.3.1.

##### 9.7.1.1.1 PRIMARY ENDPOINT

- Change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects

##### 9.7.1.1.2 SECONDARY ENDPOINTS

Change from baseline in: (revised per Amendment 02)

- Total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- The derived ADCOMS at 18 months of treatment in mild to moderate AD subjects (revised per Amendment 01)

#### 9.7.1.1.3 EXPLORATORY ENDPOINTS

(revised per Amendments 01 and 02)

Change from baseline in:

- The derived ADCOMS at 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
- Total hippocampal volume at 12 and 18 months of treatment in mild to moderate AD subjects as measured by vMRI
- CSF Aβ(1-x) and Aβ(1-42) after 4 weeks and 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ in MCI/Prodromal and mild to moderate AD subjects
- CSF biomarkers of neurodegeneration (eg, tau and p-tau) at 18 months of treatment in MCI/Prodromal and mild moderate AD subjects
- Plasma and CSF amyloid, and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild moderate AD subjects
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months in MCI/Prodromal and mild to moderate AD subjects as measured by vMRI
- Brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- The population PK parameters of E2609 including the effect of intrinsic and extrinsic factors (including *NAT2* phenotype) in MCI/Prodromal and mild to moderate AD subjects

### 9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol (PP) Analysis Set is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.

- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

#### 9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: The number (percent) of randomized and treated subjects who completed the study and who withdrew from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and withdrew from the study. The primary reasons for discontinuation from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

Completion of Study Treatment: The number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for discontinuation from the study drug are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, inadequate therapeutic response, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

#### 9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, MMSE and FAQ; categorical variables include sex, age group (≤65 years, age >65 years), race, ethnicity, *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal AD or mild to moderate AD). (revised per Amendment 01)

#### 9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up period will also be recorded.

#### 9.7.1.6 Efficacy Analyses

***The MCI/Prodromal Cohort***

The study in the MCI/Prodromal cohort is based on Bayesian adaptive design. Frequent interim analyses will be performed to assess the probability of early success and futility and to make early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis. Key definitions relevant to the Bayesian aspects of the adaptive design are given below.

**Study Definitions**

- **Maximum Effective Dose ($d_{Max}$):** The dose that achieves the greatest treatment effect.
- **$ED_{90}$:** The lowest dose that achieves at least 90% of the $d_{Max}$ treatment effect in the derived ADCOMS.
- **Early Success:** The study in the MCI/Prodromal cohort will meet early success criteria if the probability that the $ED_{90}$ at 18 months of treatment achieves 25% improvement over placebo is at least 80%. Early success is achieved before all MCI/Prodromal subjects complete 18 months of treatment and can only be determined after at least 200 MCI/Prodromal subjects have been randomized. If early success is declared before full randomization, the randomization of new MCI/Prodromal subjects will stop but subjects already randomized into the study will receive the full 18 months of treatment (following confirmation from the Sponsor's Senior Management).
- **Futility:** The study in the MCI/Prodromal cohort will meet statistical futility criteria if the probability that the $ED_{90}$ is better than placebo by the clinically significant difference of 25% is less than 5% at 18 months of treatment. The statistical futility boundary is binding; if the statistical futility boundary is crossed the study will be considered to have failed.

- **Study Success:** The study in the MCI/Prodromal cohort will be considered a success if an $ED_{90}$ at 18 months treatment has at least an 80% probability of achieving 25% improvement over placebo at either an interim analysis or at the final analysis.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

All mild to moderate AD subjects will be included in the efficacy evaluations of the Mild to Moderate AD cohort. The analysis of the Mild to Moderate AD cohort is based on the group sequential design. Interim analyses in the Mild to Moderate AD cohort will only be performed after the MCI/Prodromal cohort crosses the early success boundary. The early efficacy signal based on the change from baseline of ADCOMS at 18 months is defined as crossing the interim-analysis boundaries for overwhelming efficacy in the mild to moderate AD population. The O'Brien-Fleming (OF) boundaries based on Lan-DeMets alpha spending function will be used to assess overwhelming efficacy. The corresponding OF boundaries based on *P* values will be 0.076, 0.0221, and 0.0423 for the first, second, and final analyses, respectively, according to 2 planned interim analyses at the 60% and 80% information fraction. (revised per Amendment 01)

#### 9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

***Primary analysis of primary endpoint***

The primary analysis will be based on MCI/Prodromal subjects from the FAS with the prespecified censoring rule applied. The primary endpoint is the change from baseline to 18 months in the derived ADCOMS. The dose-response of the primary endpoint is modelled with a first-order normal dynamic linear model, where Normal and Inverse-Gamma priors are used. The primary efficacy analysis will calculate the Bayesian posterior probability that the dose identified is the most likely $ED_{90}$ dose that achieves 25% improvement over the placebo arm. At each interim analysis and the final analysis, 2 Bayesian probabilities will be summarized for each active dose: the probability it is the $ED_{90}$ dose and the probability of achieving 25% improvement over the placebo arm.

For the clinical efficacy data (ie, derived ADCOMS, MMSE, CDR, ADAS-cog, CBB, ISLT, and FAQ) subjects will be censored at the time of initiation of treatment with AChEIs or memantine, if they were not on these medications at the time of Baseline cognitive assessment (Visit 2), and will be censored at the time of dose adjustment of AChEIs or memantine if they were already on stable treatment with these medications at the time of Baseline cognitive assessment (Visit 2). The value of the primary endpoint for censored subjects will be imputed using data up to the censoring time and Bayesian longitudinal modeling.

***Sensitivity analysis of primary endpoint***

After unblinding, the primary endpoint will be analyzed using the Bayesian methods described above as well as conventional statistical methods. The following additional Bayesian analyses will be conducted as sensitivity analyses:

- The primary endpoint will be analyzed regardless of initiation of treatment, or dose adjustment, with AChEIs or memantine using the same Bayesian analysis method as primary analysis. This is an intent-to-treat analysis without any censoring.
- In case of early success, the primary analysis as well as the above sensitivity analyses will be repeated after all subjects have completed 18 months of treatment or have been lost to follow-up.

Statistical methods for the final conventional analyses will use a mixed-effects model with repeated measures (MMRM) on the change from baseline in the derived ADCOMS at 18 months. The model will include treatment groups, randomization stratification variables (the presence or absence of ongoing treatment with AChEIs or memantine or both, and *ApoE4* status), and baseline ADCOMS as covariates. Other covariates such as adjusted hippocampal volume will be studied. These analyses will be performed as sensitivity analyses on the FAS as well as the PP set and as such, no multiplicity adjustments will be made to account for the interim analyses. In case of early success, the conventional analyses will also be performed using the data collected before the interim analysis.

#### 9.7.1.6.2 SECONDARY EFFICACY ANALYSES

***The MCI/Prodromal Cohort***

An MMRM will be used to analyze the following secondary endpoint: (revised per Amendment 02)

- Change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI

Comparisons between each treatment group and placebo will be performed.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

The MMRM will be used to analyze the change from baseline of derived ADCOMS at 18 months in mild to moderate AD. If there is no treatment group-by-population interaction in the overall study, the MMRM analysis will include all subjects (MCI/Prodromal or mild to moderate AD) in the overall study. Otherwise, the MMRM analysis will only include subjects in the Mild to Moderate AD cohort. The comparison between placebo and active doses will be performed within mild to moderate AD subjects regardless of subjects included in the MMRM analysis. Dunnett's method will be used to control for multiplicity due to multiple comparisons.

#### 9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

(revised per Amendments 01 and 02)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in the derived ADCOMS at 12 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in total hippocampal atrophy at 12 and 18 months in mild to moderate AD subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) after 4 weeks and 18 months in MCI/Prodromal and mild to moderate AD subjects. Data from early discontinuations will also be included.
- Change from baseline in the clinical assessments: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in plasma and CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and 18 months as measured by vMRI in MCI/Prodromal and mild to moderate AD subjects

A linear mixed-model will be used to analyze the following exploratory endpoints:

- Change from baseline in brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in CSF biomarkers of neurodegeneration (eg, tau, p-tau) at 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects

Data from early discontinuations will also be used as appropriate. Comparisons between each treatment group and placebo will be performed.

A linear mixed-model with repeated measures will be used to determine the relationship between the following endpoints:

- Change from baseline in the derived ADCOMS score and the change from baseline in biomarkers in CSF at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in the derived ADCOMS score and change from baseline in imaging biomarkers (hippocampal, whole brain, and total ventricular volumes) at 12 and 18 months in MCI/Prodromal and mild to moderate AD subjects

*ApoE* status for heterozygous and homozygous E4 carriers will be included in the model to assess the effect of *ApoE* status in this relationship.

#### 9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

##### 9.7.1.7.1 PHARMACOKINETIC ANALYSES

The Safety Analysis Set will be used for individual E2609 concentration listings. The PK Analysis Set will be used for summaries of E2609 concentrations.

##### 9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Pharmacodynamic, PGx, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate statistical analysis plan. Please also refer to Appendix 3.

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). CSF Aβ(1-x), Aβ(1-42), t-tau, p-tau, and BACE1 will be assessed and data will be presented graphically. Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status.

Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels and exposure to E2609 in CSF will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. The PK/PD relationship between plasma PK parameters with other biomarkers may also be explored using similar methods.

Additionally, the relationship between plasma and CSF exposure to E2609 and the derived ADCOMS at 18 months, and the relationship between plasma and CSF exposure to E2609 and the change from baseline for 18 months in the ADAS-cog, the CDR, and the MMSE, will be explored graphically. Any emergent relationship will be explored through population PK/PD modeling.

Exposure-safety analyses may also be conducted.

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. The genomic DNA samples may also be stored and used as

described in Section 9.7.1.7.2. Details of PGx testing may be provided and reported separately.

#### 9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, and vital sign measurements will be summarized by treatment group using descriptive statistics.

##### 9.7.1.8.1 Extent of Exposure

The extent of exposure to study drug will be summarized as cumulative extent of exposure in 3-month intervals. The number and percent of subjects will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics in 3-month intervals. The number and percent of subjects will be presented by treatment group.

##### 9.7.1.8.2 Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 17.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and preferred term. A subject will be counted only once within an SOC and preferred term, even if the subject experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with

TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and preferred term. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

Adverse events will be summarized by the following subgroups: *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal or mild to moderate AD). (revised per Amendment 01)

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

#### 9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

Lymphocyte subsets (ie, CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages]) and regulatory T cells will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose.

Serum IgG, IgM, and IgA will be measured and summarized in the same manner as other laboratory parameters.

#### 9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

#### 9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to the end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 msec
- QTc interval >480 msec
- QTc interval >500 msec

Change from baseline in QTc interval:

- QTc interval increases from baseline >30 msec
- QTc interval increases from baseline >60 msec

#### 9.7.1.8.6 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog$_{14}$, MMSE, CDR, and CBB (see Section 9.7.1.6).

### 9.7.2 Determination of Sample Size

#### 9.7.2.1 Sample Size Rationale in the MCI/Prodromal Cohort

Primary endpoint – derived ADCOMS

The sample size and design characteristics to test the hypothesis for the primary objective based on the primary endpoint, change from baseline of the derived ADCOMS at 18 months, were determined by means of simulations. Extensive study simulations have shown that a total of 500 subjects will be sufficient to demonstrate that the most likely $ED_{90}$ dose achieves a 25% improvement over placebo with a probability of at least 80% in the interim and final analyses. There is at least a 90% probability of study success for the dose response scenarios where treatment was considered to have a clinically meaningful treatment effect. Simulations have also shown that if there is no obvious dose effect, the probability of falsely claiming superiority to placebo is at most 5%.

For each of the 4 treatment groups (3 active doses and placebo) the final number of subjects per group will differ depending on the observed interim treatment responses. The simulation plan will be an appendix to the statistical analysis plan and will present further details.

vMRI

The null hypothesis is that there is no difference between active dose and placebo. There are 3 null hypotheses corresponding to 3 active doses. The alternative hypothesis is that at least 1 null hypothesis is false (1-sided). The null hypotheses will be tested using Dunnett's method with 1-sided alpha of 0.05. The statistical power was estimated through simulation for a moderate dose-response assumption that the percent reduction in change from baseline of total hippocampal volume compared with placebo would be 15%, 20%, and 25% corresponding to the 3 doses, respectively. The estimated power for the actual planned study sample size is 78% at 18 months assuming an attrition rate of 20% at 18 months. Under a stronger dose-response assumption (ie, the percent reduction in change from baseline of total hippocampal volume compared with placebo is twice as much as that in the moderate dose-response assumption), the estimated power is at least 99% at 18 months.

Amyloid PET

The null and alternative hypotheses and the statistical test are the same as those for vMRI. To estimate the sample size for the amyloid PET imaging subgroup at 18 months, a common SD of the change from baseline was estimated at 0.33 and a reasonable mean difference between treatment and placebo was estimated as 0.25 (standardized uptake value ratio [SUVR]). Assuming a moderate dose-response, the best dose would achieve a difference of 0.25 (SUVR) and the middle and low doses would achieve a difference of 0.2 and 0.15 (SUVR), respectively; this would require a total of 100 subjects from all 4 arms at 18 months to achieve 80% power.

#### 9.7.2.2 Sample Size Rationale for the Mild to Moderate AD Cohort (revised per Amendment 01)

ADCOMS at Month 18

The null hypothesis is that there is no difference between active dose and placebo. There are 2 null hypotheses corresponding to 2 active doses. The alternative hypothesis is that at least 1 null hypothesis is false. The null hypotheses will be tested using Dunnett's test with 2-sided alpha of 0.05 as described for the Mild to Moderate AD cohort in Section 9.7.1.6.2. The statistical power was estimated through simulation for the dose-response assumption that the percent reduction in change from baseline of ADCOMS at 18 months compared with placebo would be 33% and 50% corresponding to the 2 doses, respectively. The estimated power for the actual planned 200 mild to moderate AD subjects is approximately 80% assuming a 2-sided alpha of 0.05. (revised per Amendment 01)

### 9.7.3 Interim Analysis

An interim safety analysis will be conducted when the first 60 subjects have completed 12 weeks of treatment (or discontinue study drug early) in Stage A. (revised per Amendment 01)

***The MCI/Prodromal Cohort***

The Bayesian interim analyses and response adaptive randomization will be conducted by an unblinded external independent analysis group in accordance with the protocol. Oversight of the Bayesian interim analyses and response adaptive randomization will be conducted by an independent unblinded committee that has expertise with Bayesian adaptive design in clinical studies to ensure that the response adaptive randomization process and interim analyses perform as expected. The analysis group will provide the interim analysis outcomes to the committee at each interim analysis. The committee will ensure the integrity of the interim analysis and response adaptive randomization process through review of efficacy data. In addition, the committee will act in an independent advisory capacity to monitor the Bayesian interim analysis outcomes according to the early success and futility boundaries prespecified in the protocol. The committee will not be charged with any subject safety issues; this will remain the responsibility of the DSMB.

If the predefined early success criteria are met during the recruitment period, further recruitment and enrollment of MCI/Prodromal subjects into the study will stop (following confirmation from the Sponsor's Senior Management) and all currently randomized subjects will complete the full 18 months of treatment. No further interim analyses will be conducted after achieving early success.

If the predefined threshold for futility is reached, no additional subjects will be randomized into the study and the treatment of subjects already randomized into the study will stop and the study will be declared as "failed". All subjects will be monitored for safety for 3 months following their last dose.

If neither early success nor futility is reached and the study reaches full randomization, all subjects will complete 18 months of treatment. Interim efficacy analyses will be conducted every 3 months after full randomization is reached to assess futility and early success until all subjects complete 18 months of treatment. After full randomization, all study subjects will stop treatment only in the event of futility.

The DSMB will continue to monitor the safety aspects of the study throughout Stage A and Stage B. Details will be provided in the DSMB Charter. The study may be stopped for safety at any time.

The first Bayesian adaptive interim analysis will be conducted when 100 MCI/Prodromal subjects have been randomized into the study (ie, including MCI/Prodromal subjects from Stage A and Stage B). (revised per Amendment 01) Further interim efficacy analyses will be conducted after each additional 50 MCI/Prodromal subjects have been randomized, to a maximum of 500 MCI/Prodromal subjects (ie, at 100, 150, 200, 250, 300, 350, 400, 450, 500 subjects randomized). If the study reaches full randomization, additional interim analyses will be conducted every 3 months until all subjects complete 18 months of treatment. The study will be monitored for futility at each interim analysis. Starting at the interim analysis for 200 subjects, the study will be monitored for success at each interim analysis. Each interim analysis will be conducted on data for the derived ADCOMS.

In addition, at each interim efficacy analysis, response adaptive randomization will be used to update the allocation of new subjects between placebo and active doses according to a predefined automated algorithm.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

A group sequential design will be used for the Mild to Moderate AD cohort. (revised per Amendment 01) This design includes 3 looks, 2 interim looks (when 60% and 80% information fractions are achieved) and 1 final look. The information fraction is the number of assessments in all treatment arms divided by the total number of expected assessments. Interim analyses will be performed after the MCI/Prodromal cohort crosses the early success boundary. The corresponding efficacy boundaries will be 0.076, 0.022, and 0.0423 for the first, second, and final analyses, respectively. If the actual information fraction during the

interim analyses is different from 60% or 80% at the interim, the efficacy boundaries will be adjusted based on the actual information fraction.

If early success in the MCI/Prodromal cohort is not achieved before the final analysis that is performed when all subjects have completed 18 months treatment, then only a final analysis will be performed in mild to moderate AD subjects. In the event of futility in the MCI/Prodromal cohort, an analysis will be performed for the Mild to Moderate AD cohort based on the data for mild to moderate AD subjects available at that time. (revised per Amendment 01)

Randomization into the Mild to Moderate AD cohort will remain at a fixed schedule throughout Stage B. (revised per Amendment 01)

The interim analyses in the Mild to Moderate AD cohort will be conducted by an independent analysis group. (revised per Amendment 01)

### 9.7.4 Other Statistical/Analytical Issues

**Adaptive Randomization in the MCI/Prodromal Cohort**

Randomization to placebo or 1 of 3 dose groups of E2609 will be fixed for the first 100 MCI/Prodromal subjects randomized in the study (1:1:1:1; placebo to each of the 3 active doses for the first 100 MCI/Prodromal subjects randomized, including those randomized from both Stage A and Stage B). Thereafter, randomization probabilities to each treatment group will be updated at each interim analysis, such that the randomization probability will be increased for the placebo group and dosage groups that represent the potential target dose ($ED_{90}$), and simultaneously decreased for other active arms. (revised per Amendment 01)

**Randomization in the Mild to Moderate AD Cohort** (revised per Amendment 01)

In Stage A, the mild to moderate AD subjects will be randomized to placebo or 1 of 3 E2609 dose groups (5, 15, and 50 mg of E2609) at a 1:1:1:1 ratio, while in Stage B, the mild to moderate AD subjects will be randomized to placebo or 1 of 2 E2609 dose groups (15 and 50 mg E2609) at a 1:1:1 ratio. (revised per Amendment 01)

**Stratification** (revised per Amendment 01)

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

### 9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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# 11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

## 11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

## 11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

## 11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

## 11.4 Recording of Data

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document, except when a section of the eCRF itself is used as the source document. Any correction to entries made on the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each eCRF. The investigator will report the eCRFs to the sponsor and retain a copy of the eCRFs.

## 11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents.

## 11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

## 11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

## 11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

## 11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

## 11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or CTA executed between the institution/investigator and the sponsor/CRO.

## 11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

## 11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

# 12 APPENDICES

## Appendix 1 Sponsor's Grading for Laboratory Values

(revised per Amendment 01)

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **BLOOD/BONE MARROW** | | | | |
| Hemoglobin (conversion from g/dL×0.6206) | **Female** (ULN=15.9 g/dL)<br><11.1 – 10.0 g/dL<br><111 – 100 g/L<br><6.9 – 6.2 mmol/L<br>**Male** (ULN=17.7 g/dL)<br><12.6 – 10.0 g/dL<br><126 – 100 g/L<br><7.8 – 6.2 mmol/L | <10.0 – 8.0 g/dL<br><100 – 80 g/L<br><6.2 – 4.9 mmol/L | <8.0 g/dL<br><80 g/L<br><4.9 mmol/L;<br>transfusion indicated | life-threatening consequences; urgent intervention indicated |
| Leukocytes (total white blood cell) | <3.40 – 3.0×$10^9$/L<br><3.40 $10^3$/uL – 3000/$mm^3$<br>(ULN=10.80 $10^3$/μL) | <3.0 – 2.0×$10^9$/L<br><3000 – 2000/$mm^3$ | <2.0 – 1.0×$10^9$/L<br><2000 – 1000/$mm^3$ | <1.0×$10^9$/L<br><1000/$mm^3$ |
| Lymphocytes | not applicable | <700 – 500/$mm^3$<br><0.7 – 0.5×$10^9$/L | <500 – 200/$mm^3$<br><0.5 – 0.2×$10^9$/L | <200/$mm^3$<br><0.2×$10^9$/L |
| Neutrophils | not applicable | <1.4 – 1.0×$10^9$/L<br><1400 – 1000/$mm^3$ | <1.0 – 0.5×$10^9$/L<br><1000 – 500/$mm^3$ | <0.5×$10^9$/L<br><500/$mm^3$ |
| Platelets | <155 – 75.0×$10^9$/L<br><155 $10^3$/uL – 75,000/$mm^3$<br>(ULN=379 $10^3$/μL) | <75.0 – 50.0×$10^9$/L<br><75,000 – 50,000/$mm^3$ | <50.0 – 25.0×$10^9$/L<br><50,000 – 25,000/$mm^3$ | <25.0×$10^9$/L<br><25,000/$mm^3$ |
| **METABOLIC/LABORATORY** | | | | |
| Albumin, serum- low (hypoalbuminemia) | **2 - 59 years** (ULN=5.5 g/dL)<br><3.5 – 3 g/dL<br><35 – 30 g/L<br>**59 -69 years** (LLN-ULN)<br><3.6 g/dL – 3 g/dL<br>**69 -79 years** (LLN-ULN)<br><3.5g/dL – 3g/dL<br>**79 -89 years** (LLN-ULN)<br><3.5g/dL – 3g/dL | <3 – 2 g/dL<br><30 – 20 g/L | <2 g/dL<br><20 g/L | life-threatening consequences; urgent intervention indicated |
| Alkaline phosphatase | **Female:**<br>**18 -19 years**<br>>101 – 3.0×101<br>**19 -61 years**<br>ULN=107<br>**61 -71 years**<br>ULN=112<br>**71 -150 years**<br>ULN=108<br>**Male**<br>**18 -19 years**<br>>127 – 3.0×127<br>**19 -61 years**<br>ULN=102<br>**61 -71 years**<br>ULN=103<br>**71 -150 years**<br>ULN=105 | >3.0 – 5.0×ULN<br>See previous column for ULN values | >5.0 – 20.0×ULN<br>See previous column for ULN values | >20.0×ULN<br>See previous column for ULN values |
| Alanine aminotransferase | **Female:**<br>>32 – 3.0×32<br>**Male:**<br>>44 – 3.0 x 44 | **Female:**<br>>3.0 – 5.0×32<br>**Male**<br>>3.0 – 5.0×44 | **Female:**<br>>5.0 – 20.0×32<br>**Male:**<br>>5.0 – 20.0×44 | **Female:**<br>>20.0×32<br>**Male:**<br>>20.0×44 |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Aspartate aminotransferase | >40 – 3.0×40 | >3.0 – 5.0×40 | >5.0 – 20.0×40 | >20.0×40 |
| Bilirubin (hyperbilirubinemia) | >1.2 – 1.5×1.2 | >1.5 – 3.0×1.2 | >3.0 – 10.0×1.2 | >10.0×1.2 |
| Calcium, serum-low (hypocalcemia) (conversion to mmol×0.25) | <8.5 – 8.0 mg/dL<br><2.13 – 2.0 mmol/L | <8.0 – 7.0 mg/dL<br><2.0 – 1.75 mmol/L | <7.0 – 6.0 mg/dL<br><1.75 – 1.5 mmol/L | <6.0 mg/dL<br><1.5 mmol/L |
| Calcium, serum-high (hypercalcemia) | >10.6 – 11.5 mg/dL<br>>2.65 – 2.9 mmol/L | >11.5 – 12.5 mg/dL<br>>2.9 – 3.1 mmol/L | >12.5 – 13.5 mg/dL<br>>3.1 – 3.4 mmol/L | >13.5 mg/dL<br>>3.4 mmol/L |
| Cholesterol, serum-high (hypercholesterolemia) (conversion to mmol/L ×0.02586) | **0 -19 years**<br>>169 – 300 mg/dL<br>>4.37 – 7.75 mmol/L<br>**19 -150 years**<br>>199 – 300 mg/dL<br>>5.15 – 7.75 mmol/L | >300 – 400 mg/dL<br>>7.75 – 10.34 mmol/L | >400 – 500 mg/dL<br>>10.34 – 12.92 mmol/L | >500 mg/dL<br>>12.92 mmol/L |
| Creatinine | **Female**<br>>1.00 mg/dL – 1.5×1.00<br>**Male**<br>>1.27 mg/dL – 1.5×1.27 | **Female**<br>>1.5 – 3.0×1.00<br>**Male**<br>>1.5 mg/dL – 3.0×1.27 | **Female**<br>>3.0 – 6.0×1.00<br>**Male**<br>>3.0 mg/dL – 6.0 ×1.27 | **Female**<br>>6.0×1.00<br>**Male**<br>>6.0×1.27 |
| Gamma glutamyl transpeptidase | **Female**<br>>60 IU/L – 3.0×60<br>**Male**<br>>65 IU/L – 3.0×65 | **Female**<br>>3.0 – 5.0×60<br>**Male**<br>>3.0 – 5.0×65 | **Female**<br>>5.0 – 20.0×60<br>**Male**<br>>5.0 – 20.0×65 | **Female**<br>>20.0×60<br>**Male**<br>>20.0×65 |
| Glucose, serum-high (hyperglycemia) (conversion to mmol/L ×0.0555) | **Fasting glucose value**<br>>99 – 160 mg/dL<br>>5.5 – 8.9 mmol/L | **Fasting glucose value**<br>>160 – 250 mg/dL<br>>8.9 – 13.9 mmol/L | >250 – 500 mg/dL;<br>>13.9 – 27.8 mmol/L;<br>hospitalization indicated | >500 mg/dL;<br>>27.8 mmol/L;<br>life-threatening consequences |
| Glucose, serum-low (hypoglycemia) | <65 – 55 mg/dL<br><3.6 – 3.0 mmol/L | <55 – 40 mg/dL<br><3.0 – 2.2 mmol/L | <40 – 30 mg/dL<br><2.2 – 1.7 mmol/L | <30 mg/dL<br><1.7 mmol/L<br>life-threatening consequences;<br>seizures |
| Phosphate, serum-low (hypophosphatemia) (conversion to mmol/L ×0.323) | not applicable | <2.5 – 2.0 mg/dL<br><0.8 – 0.6 mmol/L | <2.0 – 1.0 mg/dL<br><0.6 – 0.3 mmol/L | <1.0 mg/dL<br><0.3 mmol/L<br>life-threatening consequences |
| Potassium, serum-high (hyperkalemia) | not applicable | >5.5 – 6.0 mmol/L | >6.0 – 7.0 mmol/L<br>hospitalization indicated | >7.0 mmol/L<br>life-threatening consequences |
| Potassium, serum-low (hypokalemia) | <3.5 mEq/L – 3.0 mmol/L | <LLN – 3.0 mmol/L;<br>symptomatic; intervention indicated | <3.0 – 2.5 mmol/L<br>hospitalization indicated | <2.5 mmol/L<br>life-threatening consequences |
| Sodium, serum-high (hypernatremia) | >144 mEq/L – 150 mmol/L | >150 – 155 mmol/L | >155 – 160 mmol/L<br>hospitalization indicated | >160 mmol/L<br>life-threatening consequences |
| Sodium, serum-low (hyponatremia) | <134 mEq/L – 130 mmol/L | Not applicable | <130 – 120 mmol/L | <120 mmol/L<br>life-threatening consequences |
| Triglyceride, serum-high (hypertriglyceridemia) | 150 – 300 mg/dL<br>1.71 – 3.42 mmol/L | >300 – 500 mg/dL<br>>3.42 – 5.7 mmol/L | >500 – 1000 mg/dL<br>>5.7 – 11.4 mmol/L | >1000 mg/dL<br>>11.4 mmol/L<br>life-threatening consequences |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Uric acid, serum-high (hyperuricemia) | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | Not applicable | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | >10 mg/dL<br>>0.59 mmol/L<br>life-threatening consequences |

LLN = lower limit of normal, ULN = upper limit of normal.

# Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, Listing 3, Listing 4, Listing 5, and Listing 6. Medications permitted with restrictions are listed in Listing 7, Listing 8, and Listing 9. **These may not be all-inclusive listings.** Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-202 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 9 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

## Prohibited Prior/Concomitant Medications

### Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Prohibited from 14 days (or 5 half-lives, whichever is longer) before Randomization until after the last treatment visit** | | |
| **Anti-arrhythmic/ abnormal heart rhythm** | | |
| Amiodarone | Cordarone; Pacerone | Incidence in females greater than males, Torsades de Pointes risk regarded as low |
| Disopyramide | Norpace | Incidence in females greater than males |
| Dofetillide | Tikosyn | |
| Ibutilide | Corvert | Incidence in females greater than males |
| Procainamide | Pronestyl; Procan | |
| Quinidine | Cardioquin; Quinaglute | Incidence in females greater than males |
| Sotalol | Betapace | Incidence in females greater than males |
| **Antihistamine/ allergic rhinitis** | | |
| Astemizole | Hismanal | No longer available in United States |
| Terfenadine | Seldane | No longer available in United States |
| **Anti-anginal/ heart pain** | | |
| Bepridil | Vascor | Incidence in females greater than males |
| **Antibiotic/ bacterial infection** | | |
| Clarithromycin | Blaxin | |
| Moxifloxacin | Avelox | |
| Sparfloxadin | Zagam | |
| **Listing 1 continued** | | |
| **Antimalarial/ malaria infection** | | |
| Chloroquine | Aralen | |
| Halofantrine | Halfan | Incidence in females greater than males |
| **Antipsychotic/ anti-emetic/ schizophrenia/ nausea** | | |
| Chloropromazine | Thorazine | |
| **Gastrointestinal stimulant/ heartburn** | | |
| Cisapride | Propulsid | |
| **Antinausea/ nausea** | | |

## Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| Domperidone | Motillum | Not available in the United States |
| **Sedative; antinausea/ anesthesia adjunct, nausea** | | |
| Droperidol | Inapsine | |
| **Antibiotic; gastrointestinal stimulant/ bacterial infection; increase gastrointestinal motility** | | |
| Erythromycin | Erythrocin; E.E.S. | Incidence in females greater than males |
| **Antipsychotic/ schizophrenia** | | |
| Haloperidol | Haldol | When given intravenously or at higher than recommended doses, risk of sudden death, QT prolongation, and torsades increases |
| Mesoridazine | Serentil | |
| Thioridazine | Mellaril | |
| **Opiate agonist/ pain control, narcotic dependence** | | |
| Levomethadyl | Orlaam | |
| Methadone | Methadose; Dolophine | Incidence in females greater than males |
| **Anti-infective/ pneumocystis pneumonia** | | |
| Pentamidine | Pentam; NebuPent | Incidence in females greater than males |
| **Antipsychotic/ Tourette's tics** | | |
| Pimozide | Orap | Incidence in females greater than males |
| **Antilipemic/ hypercholesterolemia** | | |
| Probucol | Lorelco | No longer available in United States |
| **Anticancer** | | |
| Arsenic trioxide | Trisenox | Used for leukemia |
| Vandetanib | Zactima | Used for thyroid cancer |

Note: This list is not exhaustive.
QTc = Corrected QT interval.

## Listing 2 Prohibited Medications Within 7 Days (or 5 Half-lives, Whichever is Longer) Before Randomization and Until after the Last Treatment Visit)

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Anticoagulants** | |
| Adeporin | Normiflo |
| Alteplase, tPA | Activase, Cathflo Activase |
| Anisindione | Miradon |
| Antithrombin III | ATryn, Thrombate III |
| Argatroban | Argatroban |
| Bivalirudin | Angiomax |
| Dabigatran | Pradaxa |
| Dalteparin | Fragmin |
| Danaparoid | Orgaran |
| Dicumarol | Dicumarol |
| Enoxaparin | Lovenox |
| Fondaparinux | Arixtra |
| Heparin Sodium | Monoject |
| Lanoteplase | Lanoplase |
| Lepirudin | Refludan |
| Pentosan polysulfate sodium | Elmiron |
| Reteplase | Retavase, Retevase |
| Staphylokinase | Eskinase, Heberkinasa Kabikinase, Streptase, Thrombosolv, Zykinase |
| Streptokinase | Streptase |
| Tenecteplase | TNKase |
| Tinzaparin | Innohep |
| Urokinase | Abbokinase, Kinlytic |
| Warfarin | Coumadin, Jantoven |
| **Antiplatelet drugs** | |
| Aspirin and Plavix (revised per Amendment 01) | For subjects who consent to CSF sample collection: Aspirin or clopidogrel is permitted in all subjects. Aspirin and clopidogrel in combination is not permitted. (revised per Amendments 01 and 02)<br>For subjects who do not consent to CSF sample collection: Aspirin and clopidogrel, individually or in combination, is permitted. (revised per Amendment 02) |

Note: This list is not exhaustive.

## Listing 3 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Randomization and Until after the Last Treatment Visit

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Systemic Immunosuppressants[a] and Immunomodulatory therapy** | |
| Azathioprine | Azasan, Imur |
| Ciclosporine | Gengraf, Neoral |
| Dexamethasone | Decadron, Dexasone, Diodex, Hexadrol, Maxidex |
| Fingolimod | Gilenya |
| Methotrexate | Trexall |
| Methylprednisolone | Medrol, Meprolone |
| Mycophenolate | CellCept, Myfortic |
| Prednisolone | Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS |

Note: This list is not exhaustive.

a: Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

## Listing 4 Prohibited Medications Within 6 Months Before Randomization

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Immunoglobulin therapy** | |
| Adalimumab | Humira |
| Bevacizumab | Avastin |
| Efalizumab | Raptiva |
| Etanercept | Enbrel |
| Immune globulin IV, IVIG, IGIV | Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S |
| Infliximab | Remicade |
| Omalizumab | Xolair |
| Ranibizumab | Lucentis |
| Other monoclonal antibodies not listed here | |

Note: This list is not exhaustive.

## Listing 5 Prohibited Live Vaccines Within 3 Months Before Randomization Until after the Last Treatment Visit (this does not apply to non-live/inactivated vaccines)

| **Bacterial vaccines** | **Viral vaccines** |
|---|---|
| Bacillus Calmette-Guérin vaccine against tuberculosis | Measles vaccination |
| Cholera vaccination (oral) | Rubella vaccination |
| | Oral polio vaccination (Sabin) |
| | Yellow fever vaccination |
| | Varicella (chickenpox) vaccination |
| | Rotavirus vaccination |
| | Japanese encephalitis vaccination |
| | Live attenuated influenza vaccine (FluMist, Fluenz) |
| Typhoid vaccination (oral) | Mumps vaccination |

Note: This list is not exhaustive

## Listing 6 Strong CYP3A4 Inhibitors Prohibited Within 5 Half-Lives or 14 Days (Whichever Is Longer) Before Randomization Until After the Last Treatment Visit

| Generic name | Brand name(s) |
|---|---|
| boceprevir | Victrelis |
| clarithromycin | Clarithromycin, clarithromycin extended release, Prevpac |
| cobicistat | Tybost, Stribild, |
| conivaptan | Vaprisol |
| danoprevir | |
| elvitegravir | Vitekta, Stribild |
| indinavir | Crixivan |
| itraconazole | Sporanoz, Onmel |
| ketoconazole | Xolegel, Nizoral, Ketodan |
| lopinavir | Kaletra |
| nefazodone | Serzone |
| nelfinavir | Viracept |
| posaconazole | Noxafil |
| ritonavir | Norvir, Kaletra |
| saquinavir | Invirase, Fortovase |
| telaprevir | Incivek |
| telithromycin | Ketek |
| tipranavir | Aptivus |
| troleandomycin | Triocetin |
| voriconazole | Vfend, Voriconazole |

Note: This list is not exhaustive

## Permitted Prior/Concomitant Medications

### Listing 7 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Baseline Cognitive Assessments at Visit 2 and Remain on the Same Stable Dose from Baseline to Follow-Up Visit 2

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Cognitive Enhancers** | |
| Donepezil | Aricept |
| Galantamine | Reminyl |
| Memantine | Namenda |
| Rivastigmine | Exelon |

Note: This list is not exhaustive.

## Listing 8 Permitted Medications Used on PRN Basis Which are Not to be Used Within 72 Hours before Cognitive Testing

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Opiates** | |
| Morphine | Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol |
| **Opiate Agonists** | |
| Codeine | Codeine |
| Fentanyl | Actiq, Duragesic, Fentora, Onsolis, Sublimaze |
| Meperidine | Demerol, Meperitab |
| Oxycodone | Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol |
| Other opioids or opioid agonists which are used on PRN basis | |
| **Benzodiazepines and sedatives** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Amitriptyline | (various) |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Dothiepin | (various) |
| Estazolam | ProSom |
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |
| Lorazepam | Ativan |
| Midazolam | Versed |
| Olanzapine | Zyprexa |
| Promethazine | Phenergan; others |
| Ramelteon | Rozerem |
| Risperidone | Risperdal |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zolpidem | Ambien; others |
| Zopiclone | (various) |
| Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives | |

Note: This list is not exhaustive

PRN = Pro re nata

## Listing 9 Permitted Centrally Active or Psychiatric Medications

| **Generic Name** | **Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™)** |
|---|---|
| If to be used on a PRN basis see Listing 8. If to be used chronically, subjects must be on a stable dose for ≥4 weeks before Baseline. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks. | |
| **Antidepressants** | |
| Amitriptyline hydrochloride | Elavil |
| Amoxapine | Amoxapine |
| Bupropion | Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin |
| Citalopram | Celexa |
| Clomipramine hydrochloride | Anafranil |
| Desipramine hydrochloride | Norpramin |
| Desvenlafaxine | Pristiq |
| Doxepin hydrochloride | Prudoxin, Silenor, Sinequan, Zonalon |
| Duloxetine | Cymbalta |
| Escitalopram | Lexapro |
| Fluoxetine | Prozac, Sarafem, Selfemra |
| Fluvoxamine | Luvox |
| Imipramine hydrochloride | Tofranil |
| Isocarboxazid | Marplan |
| Maprotiline hydrochloride | Ludiomil |
| Mirtazapine | Remeron Soltab |
| Nortriptyline hydrochloride | Aventyl, Pamelor |
| Paroxetine | Paxil, Pexeva |
| Phenelzine | Nardil |
| Protriptyline hydrochloride | Vivactil |
| Rasagiline | Azilect |
| Selegiline | EMSAM |
| Sertraline | Sertaraline, Zoloft |
| Tranylcypromine | Parnate |
| Trazodone hydrochloride | Desyrel, Oleptro |
| Trimipramine maleate | Surmontil |
| Venlafaxine hydrochloride | Effexor |

## Listing 9 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Mood Stabilizers (Listing 8 continued)** | |
| Carbamazepine | Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR |
| Lamotrigine | Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR |
| Valproic acid | Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate |
| **Antipsychotics** | |
| Acetophenazine | Tindal |
| Aripiprazole | Abilify |
| Asenapine | Saphris |
| Olanzapine | Zyprexa |
| Chlorpromazine | Thorazine |
| Haloperidol | Haloperidol, Haldol |
| Clozapine | Clozaril, Fazaclo |
| Fluphenazine | Prolixin |
| L-Methylfolate | Deplin, L-Methylfolate Calcium |
| Loxapine | Loxitane |
| Mesoridazine | Serentil |
| Perphenazine | Trilafon |
| Quetiapine | Seroquel |
| Risperidone | Risperdal |
| Thioridazine | Mellaril |
| Thiothixene | Navane |
| Trifluoperazine | Stelazine |
| **Benzodiazepines** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Estazolam | ProSom |
| Flunitrazepam | Rohypnol |

## Listing 9 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| Flurazepam | Dalmane |
| Lorazepam | Ativan |
| Midazolam | Versed |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zopiclone | Imovane, Zimovane |
| Zopidem | Ambien, Ambien CR, Intermezzo, Stilnox, Stilnoct, Sublinox, Hypnogen, Zolsana |

Note: This list is not exhaustive.

PRN = Pro re nata

# Appendix 3 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

## Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

## Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In

this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

### Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

### Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed

scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

# Appendix 4 AEs Indicating Signals of Possible Drug Abuse Potential

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| 1 | **Euphoric mood** | Euphoric mood |
| | | Euphoria |
| | | Euphoric |
| | | Exaggerated well-being |
| | | Excitement excessive |
| | | Feeling high |
| | | Felt high |
| | | High |
| | | High feeling |
| | | Laughter |
| 2 | **Elevated mood** | Elevated mood |
| | | Mood elevated |
| | | Elation |
| 3 | **Feeling abnormal** | Feeling abnormal |
| | | Cotton wool in head |
| | | Feeling dazed |
| | | Feeling floating |
| | | Feeling strange |
| | | Feeling weightless |
| | | Felt like a zombie |
| | | Floating feeling |
| | | Foggy feeling in head |
| | | Funny episode |
| | | Fuzzy |
| | | Fuzzy head |
| | | Muzzy head |
| | | Spaced out |
| | | Unstable feeling |
| | | Weird feeling |
| | | Spacey |
| 4 | **Feeling drunk** | Feeling drunk |
| | | Drunkenness feeling of |
| | | Drunk-like effect |
| | | Intoxicated |
| | | Stoned |
| | | Drugged |
| 5 | **Feeling of relaxation** | Feeling of relaxation |
| | | Feeling relaxed |
| | | Relaxation |
| | | Relaxed |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Increased well-being |
| | | Excessive happiness |
| **6** | **Thinking abnormal** | Thinking abnormal |
| | | Abnormal thinking |
| | | Thinking irrational |
| | | Thinking disturbance |
| | | Thought blocking |
| | | Wandering thoughts |
| **7** | **Hallucination** | Hallucination |
| | | Illusions |
| | | Flashbacks |
| | | Floating |
| | | Rush |
| | | Feeling addicted |
| **8** | **Inappropriate affect** | Elation inappropriate |
| | | Exhilaration inappropriate |
| | | Feeling happy inappropriately |
| | | Inappropriate affect |
| | | Inappropriate elation |
| | | Inappropriate laughter |
| | | Inappropriate mood elevation |
| **9** | **Mood disorders and disturbances** | Mental disturbance |
| | | Depersonalisation |
| | | Psychomotor stimulation |
| | | Mood disorders |
| | | Emotional and mood disturbances |
| | | Delirium |
| | | Delirious |
| | | Mood altered |
| | | Mood alterations |
| | | Mood instability |
| | | Mood swings |
| | | Emotional lability |
| | | Emotional disorder |
| | | Emotional distress |
| | | Personality disorder |
| | | Impatience |
| | | Abnormal behavior |
| | | Delusional disorder |
| | | Irritability |
| **10** | **Drug tolerance** | Drug tolerance |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Habituation |
| | | Drug withdrawal syndrome |
| | | Substance-related disorders |
| **11** | **Psychosis** | Psychosis |
| | | Psychotic episode or disorder |
| **12** | **Dissociative State** | Dissociation |
| | | Disconnected |
| | | Derealisation |
| | | Depersonalisation |
| | | Detached |
| | | Sensation of distance from one's environment |
| | | Loss of a sense of personal identity |

# Appendix 5 Eisai Lymphocyte Subset Criteria for Study E2609-G000-202: Justification for a Population-Adjusted Approach

**Introduction:**

The Eisai clinical study, E2609-G000-202, requires the analysis of absolute numbers of various functional subsets of circulating lymphocytes. These are distinguished by identification of various complementary differentiation (CD) markers on the cell surface using fluorescent-labeled antibody reagents and flow cytometry. Current enumeration of certain lymphocyte subsets form part of the immunologically based eligibility criteria for study enrollment, as well as being monitored for safety for enrolled and treatment randomized subjects. The Trucount™ M (Becton, Dickinson and Company [BD], BD Biosciences, San Jose, CA) antibody reagents used for the lymphocyte subset eligibility criteria, provides readouts for both absolute (BD Trucount tubes) and percentage of lymphocyte subsets, and includes the following CD markers: CD3 (T cells), CD4 (T helper cells), CD8 (cytotoxic T cells), CD16/56 (natural killer cells), CD14 (macrophages), and CD19 (B cells).

Trucount lymphocyte subset reference ranges provided by the reagent manufacturer (BD) for both absolute and percentages were established for clinical use as an in vitro diagnostic using standardized reference interval methodology. These LLN for the various lymphocyte subsets are currently being used by the central laboratory for Eisai Study E2609-G000-202 to determine eligibility of screened subjects and as part of safety assessments during post-randomization visits. The eligibility criterion excludes subjects with absolute counts of T and B cell markers (CD4, CD8, and CD19 respectively) less than the reference range lower limit of normal (<LLN) at Screening or Baseline.

**Need to assign age appropriate reference ranges:**

Reference ranges established by the vendor according to working group guidance[3] may not be representative of different subgroup analyses (eg, ancestry, disease state, age, gender, etc.), and therefore interval adjustment may be required depending on the subpopulation of interest. The working group guidance for reference intervals (CLSI, 2010[4]) recommends examining data to determine if >10% of subjects are outliers (ie, more than 10% < LLN), and if so, to initiate development of subgroup-appropriate intervals by analyzing data from the literature or internal studies representing the reference population [a minimum of 120 observations recommended by the guidance.[3]]

Data from the ongoing Study E2609-G000-202 has been examined and greater than 10% of the study population screening samples fall below the manufacturer recommended LLN for the key lymphocyte subsets. The population for Study E2609-G000-202 are patients aged 50 to 85 years old inclusive with Mild Cognitive Impairment due to AD or with Mild to Moderate dementia due to AD. Lymphocyte subset data from a data cut of 93 screened subjects was analyzed and showed that both CD8 and CD4 had greater than 10% of the

subjects with results <LLN (26.9%, <220 cells/mm$^3$ and 13%, <404 cells/mm$^3$, respectively); CD19 had approximately 10% of the subjects with results <LLN (9.7%, <80 cells/mm$^3$).

To further determine if the outlier data observations from the ongoing Study E2609-G000-202 were associated with disease status or age, lymphocyte subset data from additional Eisai studies that included healthy elderly subjects or patients diagnosed with MCI or mild/moderate AD were examined. The individuals from all 3 studies included the same 50-to 85-year-old age range as the current E2609-G000-202 study. The studies evaluated include: (1) Study E2609-A001-002 treatment study (n=50 healthy elderly); (2) Lymphocyte subset pilot study in healthy elderly [n=30]; and (3) Lymphocyte subset pilot study in AD/MCI [n=31]. Screening or baseline sample from all 4 studies had >10% of the CD8 absolute counts below reference LLN, 2 out of 4 had >10% of the CD19 absolute counts below reference LLN and 1 out of 4 had >10% of the CD4 absolute counts out of reference LLN [Table 10, Table 11, and Table 12]. The data suggests that the reference values of LLN for CD4, CD8, and CD19 subsets are not a disease-associated observation but are related to the age of the study population being evaluated.

In addition to the Eisai study data, age related decline in lymphocyte subsets has been described in the literature Yan et.al.[1][2] Analysis was performed using flow cytometry on peripheral blood leukocytes using healthy subjects across the 3rd and 10th decades of life. The results from the Yan study (n=80; 37 males, 43 females) demonstrated that with advancing age there was a significant decline in the percentage of lymphocytes, specifically naive T cells [CD3 *P*=0.03], cytotoxic T cells [CD8 *P*=0.08] and activated B cells [CD20/CD69 *P*=0.03] with certain subsets demonstrating even greater decline in males.[1] The age associated changes in immune capabilities, termed "immunosenescence", which include degenerative changes in the lymph nodes, effects on lymphocyte subsets and changes in adaptive immunity may underlie the increased risk of infection and cancer and decreased immune function in the elderly. This, along with the data from the four Eisai studies described earlier, support the readjustment of the LLNs for the CD reference ranges used for eligibility in Study E2609-G000-202 such that they are better suited to the older patient population enrolling in this study which is thought to be representative of the wider patient population.

**Determining the new LLN criteria:**

The recommended method for establishing reference intervals is the nonparametric approach where the underlying distribution of the data does not matter. The values received from the data (a minimum of 120 observations representing the subgroup population of interest is recommended) are rank ordered and can be used to evaluate the comparative reference interval.[3]

When data from the 4 Eisai studies are put in rank order (see Table 10, Table 11, and Table **12**), and a 10% cut value is applied to each of the 3 CD markers of interest the following age-adjusted LLN values are generated:

**Table 9 Summary of CD4, CD8, and CD19 LLNs and Age-Adjusted LLNs**

| Lymphocyte Subset | Current LLN | Age-adjusted LLN |
|---|---|---|
| CD4 absolute count | 404 cells/$mm^3$ | 396 cells/$mm^3$ |
| CD8 absolute count | 220 cells/$mm^3$ | 157 cells/$mm^3$ |
| CD19 absolute count | 80 cells/$mm^3$ | 74 cells/$mm^3$ |

**Table 10 Summary of CD Counts (Parameter: CD19)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 30 | 203 |
| Mean | 213.47 | 198.49 | 159.20 | 172.77 | 192.57 |
| Median | 189.66 | 163.00 | 118.50 | 159.50 | 164.86 |
| 5th percentile | 84.81 | 59.00 | 38.00 | 69.00 | 59.00 |
| 10th percentile | 102.26 | 81.00 | 42.00 | 70.50 | 74.00 |
| 25th percentile | 139.66 | 104.00 | 75.00 | 100.00 | 104.58 |
| 75th percentile | 261.51 | 225.00 | 225.00 | 246.00 | 246.00 |
| 95th percentile | 376.67 | 443.00 | 424.00 | 384.00 | 402.00 |
| Range | 66.19, 593.48 | 17.00, 1066.00 | 37.00, 455.00 | 39.00, 415.00 | 17.00, 1066.00 |

**Table 11 Summary of CD Counts (Parameter: CD8)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 31 | 204 |
| Mean | 362.72 | 352.18 | 324.63 | 427.74 | 362.20 |
| Median | 364.74 | 330.00 | 344.00 | 315.00 | 336.39 |
| 5th percentile | 115.02 | 138.00 | 86.00 | 100.00 | 115.02 |
| 10th percentile | 170.24 | 151.00 | 159.50 | 153.00 | 157.00 |
| 25th percentile | 253.37 | 213.00 | 204.00 | 217.00 | 230.00 |
| 75th percentile | 465.52 | 425.00 | 405.00 | 494.00 | 438.00 |
| 95th percentile | 614.57 | 716.00 | 557.00 | 988.00 | 702.00 |
| Range | 98.45, 702.50 | 37.00, 803.00 | 61.00, 702.00 | 54.00, 2255.00 | 37.00, 2255.00 |

**Table 12 Summary of CD Counts (Parameter: CD4)**

| | BEAM 002 | BEAM 202 | Pilot AD/MCI | Pilot Control | Combined Total |
|---|---|---|---|---|---|
| n | 50 | 93 | 30 | 31 | 204 |
| Mean | 846.15 | 839.58 | 789.27 | 804.52 | 828.46 |
| Median | 836.94 | 805.00 | 777.50 | 771.00 | 791.50 |
| 5th percentile | 388.44 | 337.00 | 395.00 | 351.00 | 344.00 |
| 10th percentile | 479.55 | 361.00 | 490.00 | 427.00 | 396.00 |
| 25th percentile | 639.54 | 620.00 | 661.00 | 669.00 | 633.77 |
| 75th percentile | 1031.49 | 1078.00 | 924.00 | 1014.00 | 1039.50 |
| 95th percentile | 1315.55 | 1404.00 | 1124.00 | 1327.00 | 1347.00 |
| Range | 274.90, 1643.55 | 197.00, 1481.00 | 248.00, 1720.00 | 143.00, 1336.00 | 143.00, 1720.00 |

References:

1. Yan et al., Immunity and Ageing 2010 v. 7:4; The effect of ageing on human lymphocyte subsets: comparison of males and females.
2. Wikby et al., Biogerontology 2008 vol 9: 299; The immune risk profile is associated with age and gender: findings from three Swedish population studies of individuals 20-100 years of age.
3. Horowitz eJIFCC 2008 vol. 19 (2) Reference intervals: practical aspects).
4. Horowitz et al., CLSI Vol 28 no. 30 Clinical and Laboratory Standards Institute's (CLSI) newly revised document Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition (C28-A3), published in November 2010 EP28-AC3

# PROTOCOL SIGNATURE PAGE

**Study Protocol Number:** E2609-G000-202
**Study Protocol Title:** A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability and Efficacy of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01)
**Investigational Product Name:** E2609
**IND Number:** 109308
**EudraCT Number:** 2014-002723-94

**SIGNATURES**
Authors:

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Eisai Inc.

Date

# INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability and Efficacy of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01) |
| **Investigational Product Name:** | E2609 |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

| Investigator | Signature | Date |
|---|---|---|

# REVISION HISTORY

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised inclusion to allow for enrollment of mild to moderate AD subjects in Stage A and expand the Stage B mild AD cohort to also include moderate AD subjects | To collect safety data in a wider range of AD patients. | • Title Page<br>• Synopsis –<br>  ○ Objectives<br>  ○ Study Design<br>  ○ Number of Subjects<br>  ○ Inclusion/Exclusion Criteria<br>  ○ Study Treatments<br>  ○ Efficacy Assessments<br>  ○ Study Endpoints<br>  ○ Efficacy Analyses<br>  ○ Interim Analyses<br>  ○ Adaptive Randomization<br>  ○ Sample Size<br>• Section 5.3<br>• Section 7<br>• Section 8 (and all subsections)<br>• Section 9.1, Section 9.1.1<br>• Figure 1<br>• Section 9.2.1, Section 9.2.2, Section 9.2.3<br>• Section 9.2.5.3 and Section 9.2.5.4<br>• Section 9.3, Section 9.3.1, Section 9.3.2<br>• Section 9.4.1, Section 9.4.3, Section 9.4.4<br>• Section 9.5.1.3.1<br>• Section 9.7.1.1.2, Section 9.7.1.1.3<br>• Section9.7.1.4<br>• Section 9.7.1.6, Section 9.7.1.6.2, Section 9.7.1.6.3<br>• Section 9.7.1.8.2<br>• Section 9.7.2.2<br>• Section 9.7.3<br>• Section 9.7.4 |
| Revised inclusion criteria for MMSE to ≥16 from ≥20 | The MMSE score is used as a cut-off for the most impaired subject that would be eligible for the study. Lowering the MMSE inclusion from ≥20 to ≥16 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD cohort. | • Synopsis – Inclusion/Exclusion Criteria<br>• Section 9.3.1 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revised inclusion criteria for FAQ to ≤24 from ≤20 | As for the MMSE, the FAQ score is used as a cut-off for the most impaired subject that would be eligible for the study. Revising the FAQ inclusion from ≤20 to ≤24 is consistent with expanding the Mild AD cohort to a Mild to Moderate AD cohort, and is consistent with an MMSE inclusion of ≥16. | • Synopsis – Inclusion/Exclusion Criteria<br>• Section 9.3.1 |
| Revised exclusion criteria such that small arachnoid cysts are not necessarily exclusionary | Arachnoid cysts are a common finding in otherwise healthy subjects. Small lesions (<1 cm in diameter) are generally not considered clinically significant and if discovered incidentally no long term follow up is routinely required. | • Synopsis – Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised exclusion criteria for Ig (IgG, IgA, or IgM) to specify that levels below the LLN at Screening or Baseline need not be exclusionary | For subjects with a Screening or Baseline IG level <LLN to be considered for continuation in the study, assessment of clinical significance of the finding will be required. A finding of "not clinically significant" must be agreed between the Investigator and Medical Monitor in order for the subject to continue in the study. | • Synopsis – Inclusion/Exclusion Criteria<br>• Section 9.3.2 |
| Revised text to provide instructions for subject assent and associated consent by a legal representative for subjects who the Investigator considers not to have the capacity to consent themselves | With the expansion of the patient population to include moderately demented subjects it was necessary to provide directions regarding the consenting process for subjects considered to be lacking the capacity to consent themselves. | • Section 5.3 |
| Revised number of clinical sites to 30 from 25 | For feasibility purposes. | • Synopsis – Sites<br>• Section 6<br>• Section 9.1<br>• Section 9.3 |
| Added allowance for Tier 1 and Tier 2 screening assessments to be performed on the same day | Added to provide operational clarity for the sites. | • Section 9.1.1.1<br>• Table 6 |

## Revisions to Version 2.0

## New version/date: Version 3.0, 28 May 2015

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Removed requirements for MRIs to include sequences for resting state functional MRI | This was an error and should not have been included in the original protocol. | • Table 6<br>• Table 7 |
| Revised text to clarify that on visits where CSF collection takes place, the CSF collection need not take place on the same day as the cognitive testing for that visit | Added to provide operational clarity for the sites. | • Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised text to clarify that the most important efficacy assessment to keep blinded from safety data is the CDR. | Added to provide operational clarity for the sites. | • Synopsis – Safety Assessments<br>• Section 9.4.6<br>• Section 9.5.1.5 |
| Revised text to allow PK blood sample and PD blood samples to be taken either shortly before or shortly after the LP on CSF days | Added to provide operational flexibility for the sites. | • Section 9.5.1.4.1<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Revised Sponsors Grading for Laboratory Values for the following analytes: lymphocytes, neutrophils, albumin, creatinine, phosphate, and potassium serum-high (hyperkalemia) | Corrections made to align with the values for grading used by the central clinical laboratory for this study. | • Appendix 1 |
| Revised details regarding prohibited antiplatelet drugs | Previous version incorrectly referenced a biomarker subgroup. All subjects in this study will need to provide CSF samples. | • Appendix 2; Listing 2 |
| Revised grammar, spelling, etc. | Compliance with current company style guide and for general consistency. | Throughout protocol |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revisions to grammar, spelling, etc. | Compliance with current company style guide and for general consistency | • Throughout protocol |
| Revisions made per new company protocol template | Alignment with current Eisai template | • Synopsis - Inclusion/Exclusion Criteria<br>• Section 9.1.2.3<br>• Section 9.3.1<br>• Section 9.3.2<br>• Section 9.5.1 (related subsections)<br>• Section 9.5.4<br>• Section 9.5.4.1<br>• Section 9.5.4.2<br>• Section 9.5.4.3 |
| Clarified classification of MCI due to AD | Clarification that MCI due to AD population will also be consistent with the research criteria for Prodromal AD in that impaired episodic memory is required and will be tested using a list learning task (the International Shopping List Task) | • Synopsis – Study Design<br>• Section 9.1 |
| Replaced "enroll" with "randomize," pertaining to subject entry into study | Correction to terminology | • Synopsis – Study Design<br>• Section 9.1<br>• Section 9.3 |
| Added criterion excluding subjects with hepatic impairment and total bilirubin greater than 1.5×ULN or INR greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded. | At request of FDA, exclude subjects who have hepatic impairment | • Synopsis – Inclusion/Exclusion Criteria<br>• Abbreviation List<br>• Section 9.3.2 |
| Added coagulation parameters for prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR) to screening and baseline procedures | Screen for hepatic impairment | • Synopsis – Inclusion/Exclusion Criteria<br>• Abbreviation list<br>• Section 9.3.2<br>• Table 4<br>• Table 6<br>• Table 8 |
| For subjects who discontinue study drug prematurely, conduct efficacy | To facilitate efficacy analyses, which are based on longitudinal | • Synopsis –Study Design<br>• Section 9.1.2.2<br>• Section 9.3.3 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| assessments postdose at same time points as subjects who continue in the study. Added FAQ to this set of efficacy assessments. | modeling for all subjects | • Section 9.5.4.1<br>• Section 9.5.5<br>• Table 7 |
| Delete diagram of E2609 structure | This display is not needed for the protocol. The Investigator's Brochure has this information. | • Section 9.4.2.1 |
| Additional blood samples to be taken at Visits 19 and 20 | Samples are to be put in storage to allow for assessment of immune status at end of study, as needed. | • Synopsis - Assessments<br>• Table 8 |
| Add subheadings to Section 9.7 describing the primary endpoint analysis, and text clarifying that no multiplicity adjustments will be done to account for the interim analyses | To distinguish clearly the primary analysis and the sensitivity analyses of the primary endpoint | • Synopsis - Efficacy Analyses<br>• Section 9.7.1.6.1 |
| Clarification of PK sampling upon Early Discontinuation | Additional operational details of the timing of the PK sampling at the ED visit provided | • Section 9.5.1.4.1<br>• Table 7 |
| Clarification of ApoE testing | Clarification that the ApoE genetic testing will be for homozygous or heterozygous E4, versus non-E4 | • Section 9.5.1.4.2 |
| Revision to PK/PD interim analysis text | Confirm that interim PK/PD analysis will be conducted by an independent group | • Section 9.4.6 |
| Addition of text regarding safety signals with E2609 | To provide information on safety-driven dose adjustments | • Synopsis – Study Design<br>• Section 9.1 |
| Addition of PBMC collection/assessment at Baseline, during treatment, and posttreatment | Recent animal studies have shown an effect of E2609 on this model so they will be added to the 202 clinical study as an additional exploratory assessment. | • Synopsis – Safety Assessments<br>• Section 9.2.6<br>• Section 9.5.1.5<br>• Table 4<br>• Table 6<br>• Table 7<br>• Table 8 |
| Stipulate that exploratory biomarker analyses may be conducted using blood or CSF samples that may have been drawn for other purposes | To allow more flexibility for possible exploratory biomarker studies associated with study drug or disease, including miRNA and DNA | • Synopsis - Assessments,<br>• Abbreviation list<br>• Section 9.5.1.4.2<br>• Section 9.5.1.5.12<br>• Table 6<br>• Table 7 |
| Prohibit concomitant medications that are strong CYP3A4, inhibitors, but clarify that no restrictions are | At request of FDA, in light of finding that inhibition of CYP3A4 by a reference agent increases | • Synopsis - Concomitant Drug/Therapy<br>• Section 7.1 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| needed for other CYP3A4 inhibitors, CYP3A4 inducers, or CES2 inhibitors | plasma levels of E2609 | • Section 9.4.7<br>• Appendix 2(Listing 6) |
| Addition of tests for viral characterization at Baseline | To confirm by serology information of subjects prior exposure to common viruses pre-dosing with study drug | • Section 9.5.1.2.2<br>• Table 4<br>• Table 6<br>• Table 8 |
| Use of a centralized dermatologist assessment via photography | A centralized approach, using standardized photography, to FDA-required serial dermatological assessments will be employed for consistency of assessments between sites and for consistency of longitudinal assessments of individual subjects. | • Synopsis – Safety Assessments<br>• Section 9.2.6<br>• Section 9.5.1.5<br>• Section 9.5.1.5.8<br>• Table 6<br>• Table 7 |
| Removal of testing for benzodiazepines or opioids as part exclusion criteria #35 | To differentiate appropriate medicinal use from recreational drug use or abuse | • Synopsis – Exclusion Criteria<br>• Section 9.3.2 |
| Addition of analysis of other covariates such as adjusted hippocampal volume will be studied | Hippocampal volume has been shown to correlate with rate of cognitive decline and as such is a key covariate to be used in the analyses. | • Synopsis – Analysis of Primary Endpoint<br>• Section 9.7.1.6.1 |
| Addition of clarifications to ophthalmic examination | To provide more detail around the requirements for the ophthalmic exam | • Synopsis – Safety Assessments<br>• Section 9.5.1.5.13<br>• Table 6<br>• Table 7 |
| Addition of details regarding specific method of CSF collection (ie, gravity drip) | Use of materials required for suction method when collecting CSF can affect the PD data and so it is important to make it clear that only the gravity drip method can be used for collecting CSF in this study for protecting the quality and the consistency of the CSF PD data. | • Section 9.5.1.3.3<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Addition of specific testing for B12 levels at Screening | Abnormally low serum vitamin B12 levels are exclusionary for the study (excl criterion 8) but a blood draw for Vit B12 was inadvertently missed out of Table 6 in protocol version 1. | • Synopsis – Exclusion Criteria<br>• Section 9.3.2<br>• Section 9.5.1.2.3<br>• Figure 2<br>• Table 6 |
| Addition of details regard AEs that might be signals of possible drug abuse potential | Changed terminology re: collection of additional information for AEs that might be signals of possible | • Synopsis – Safety Assessments<br>• Section 9.2.6<br>• Section 9.5.1.5.1 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| | abuse potential. No longer use the word "narrative" in order to avoid potential confusion with standard clinical trial narratives eg, for serious adverse events, adverse events leading to withdrawal, etc. | • Appendix 4 |
| Addition of clarification regarding position for taking vital signs (ie, supine) | The American Heart Association guidelines only mention supine, standing, and sitting as positions for taking HR and BP measurements. Therefore, have changed required position from semi-supine to sitting. | • Section 9.5.1.5.4<br>• Table 6<br>• Table 7 |
| Stipulated that study drugs are to be taken with food | For consistency of treatment conditions | • Section 9.5.1.4.1 |
| Change to list of Study Specific AEs which should be considered SAEs | Eisai's standard procedures have changed such that non-serious study specific adverse events of interest are no longer reported to Eisai Product Safety; instead, any additional information required for such non-serious adverse events will be obtained through other methods. In addition, certain events (new onset seizures, ocular herpes) are now to be classified as serious as important medical events, regardless of whether they meet standard ICH serious criteria. | • Section 9.5.1.5.1<br>• Section 9.5.1.5.2 |
| Increased blood volume for PK | To match collection tubes and ensure sufficient sample for planned assays | • Table 8 |
| Corrected error in definition of PK analysis set | For accuracy | • Synopsis – Study Endpoints<br>• Section 9.7.1.2 |
| Addition of details regarding discontinuation of study drug | To clearly and consistently differentiate "discontinuation from study drug" from "withdrawal from study" | • Synopsis<br>• Section 7<br>• Section 9.1.2.1<br>• Section 9.2.6<br>• Section 9.3.3<br>• Table 1<br>• Table 2<br>• Section 9.4.1<br>• Section 9.4.4<br>• Section 9.5.1.5.1<br>• Section 9.5.1.5.3<br>• Section 9.5.5 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Re-ordered prohibited medication lists | For consistency, all lists re-ordered in alphabetical order of generic drug name, and footnotes revised for overall consistency | • Appendix 2 |
| Moved nefazodone from Listing 9 to Listing 6 | Nefazodone is a strong CYP3A4 inhibitor and is therefore prohibited. | • Appendix 2 |

# 1 TITLE PAGE


## Clinical Study Protocol

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability, and Efficacy of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01) |
| **Sponsor:** | Eisai Inc.<br>155 Tice Boulevard<br>Woodcliff Lake,<br>New Jersey 07677<br>United States<br><br>Eisai Ltd.<br>European Knowledge Centre<br>Mosquito Way<br>Hatfield, Hertfordshire<br>AL10 9SN<br>United Kingdom<br><br>Eisai Co., Ltd.<br>4-6-10 Koishikawa<br>Bunkyo-Ku,<br>Tokyo 112 8088<br>Japan |
| **Investigational Product Name:** | E2609 |
| **Indication:** | Alzheimer's disease |
| **Phase:** | 2 |
| **Approval Date:** | V1.0 15 Jul 2014 (original protocol)<br>V2.0 21 Oct 2014 (revised original protocol)<br>V3.0 28 May 2015 (per Amendment 01) |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |
| **GCP Statement:** | This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities. |
| **Confidentiality Statement:** | This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study. |

# 2 CLINICAL PROTOCOL SYNOPSIS

**Compound No.:**
E2609

**Name of Active Ingredient:**
*N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

**Study Protocol Title**
A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability, and Efficacy of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01)

**Investigators**
Stage A: Investigators in United States only

Stage B: Multinational investigators

**Sites**
Stage A: Approximately 30 sites, United States only (revised per Amendment 01)

Stage B: Approximately 125 sites, globally

**Study Period and Phase of Development**
Stage A: Approximately 32 months and will continue and overlap with Stage B

Stage B: Approximately 42 months from initiation of Stage B (revised per Amendment 01)

Phase 2

**Objectives**
**Primary Objectives**
1. To evaluate the efficacy of daily dosing with 3 doses of E2609 compared with placebo by establishing the lowest effective dose that achieves 90% of the greatest treatment effect ($ED_{90}$) for E2609 on the derived Alzheimer's Disease Composite Score (ADCOMS) at 18 months of treatment in subjects with Mild Cognitive Impairment due to Alzheimer's Disease/ Prodromal Alzheimer's Disease (referred to as MCI/Prodromal throughout the protocol)
2. To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with Mild to Moderate Dementia due to Alzheimer's Disease (referred to as mild to moderate AD throughout the protocol) (revised per Amendment 01)

**Secondary Objectives**
1. To evaluate the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects, as measured by volumetric magnetic resonance imaging (vMRI)

2. To evaluate the effect of E2609 compared with placebo on amyloid β(1-x) (Aβ[1-x]) in cerebrospinal fluid (CSF) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
3. To evaluate the efficacy of E2609 compared with placebo on the derived ADCOMS at 18 months in mild to moderate AD subjects (revised per Amendment 01)

**Exploratory Objectives**

(revised per Amendment 01)

1. To explore the effect of E2609 compared with placebo on the derived ADCOMS following 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
2. To explore the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in mild to moderate AD subjects, as measured by vMRI
3. To explore the effects of E2609 compared with placebo on Aβ(1-42) in CSF after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
4. To explore the effects of E2609 compared with placebo on Aβ(1-x) and Aβ (1-42) in CSF after 4 weeks and 18 months of treatment in mild to moderate AD subjects
5. To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during post-treatment follow-up, in MCI/Prodromal and mild to moderate AD subjects, by assessment of:
   a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
   b. The Clinical Dementia Rating (CDR) scale
   c. The Mini-Mental State Examination (MMSE)
   d. The CogState Brief Battery (CBB)
   e. The Functional Assessment Questionnaire (FAQ; also known as the Functional Activities Questionnaire)
   f. The International Shopping List Task (ISLT)
6. To explore the effects of E2609 compared with placebo on various biomarkers in MCI/Prodromal and mild to moderate AD subjects. Biomarkers to be explored include:
   a. CSF biomarkers of neurodegeneration (eg, tau, phosphorylated-tau [p-tau]) after 18 months of treatment
   b. Plasma and CSF amyloid, and CSF β-amyloid converting enzyme 1 (BACE1) measurements during 18 months of treatment and during posttreatment follow-up
   c. vMRI measurements including left and right hippocampal volume, whole brain volume and total ventricular volume at 6, 12, and 18 months of treatment and during post-treatment follow-up
   d. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)
7. To characterize the population pharmacokinetics (PK) of E2609 in MCI/Prodromal and mild to moderate AD subjects, and to examine the effect of intrinsic and extrinsic factors (including N-acetyltransferase 2 [*NAT2*] phenotype) on the PK

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| 8. To explore the relationship between the treatment effects of E2609 on the ADCOMS and its effects on CSF amyloid, CSF BACE1, CSF tau, and vMRI in MCI/Prodromal and mild to moderate AD subjects |

**Study Design**

This will be a multicenter placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild to moderate AD. A common set of inclusion criteria, consistent with the National Institute on Aging – Alzheimer's Association (NIA-AA) clinical research criteria for Mild Cognitive Impairment (MCI) due to Alzheimer's Disease (AD) or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with the criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study will be conducted in 2 stages, Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 (after the first 60 randomized subjects have completed 12 weeks of treatment or have discontinued study drug early) before expanding enrollment to include a larger number of subjects in Stage B. (revised per Amendment 01) All MCI/Prodromal subjects will be included in the primary efficacy evaluation irrespective of whether they were recruited during Stage A or Stage B. Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B. All mild to moderate AD subjects will be included in the efficacy evaluations for that cohort. (revised per Amendment 01)

Both Stage A and Stage B will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days) includes a Screening Visit (Visit 1) and a Baseline Visit (Visit 2). All screening assessments (within 4 distinct tiers) must be completed, and eligibility to continue in the study confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

**Stage A**

Stage A will randomize 60 eligible subjects at Visit 3, 1:1:1:1 to 4 treatment groups within each of the 2 clinical populations. (revised per Amendment 01) In addition to the placebo group, 3 E2609 doses will be used to reduce CSF amyloid β levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/pharmacodynamic (PD) modeling has shown that these doses should achieve these targets when administered once daily (QD) with food, and these doses will be confirmed or adjusted based on the 4-week assessment of CSF Aβ(1-x).

During Stage A, safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the first subject is randomized during

Stage A, an independent data safety monitoring board (DSMB; including at least 1 immunologist) will review all safety data in an unblinded manner. The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. Unless the DSMB recommends otherwise, randomization of subjects into Stage A will continue until 60 subjects have been randomized and dosed. (revised per Amendment 01)

After 60 subjects in Stage A have completed 4 weeks of treatment, an interim analysis of the E2609 PK and PD profiles will be used to confirm the E2609 doses to be used for Stage B. (revised per Amendment 01) If the 95% confidence interval of the mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment with a dose of E2609 does not include its intended target value (ie, 25%, 50% and 75% reductions from baseline, respectively for E2609 at 5 mg, 15 mg, and 50 mg QD), PK/PD modeling will be conducted. From this model, the new target plasma steady state concentrations of E2609 required to achieve the target levels of CSF Aβ(1-x) reduction will be estimated again. Dose adjustment for Stage B may be considered if it is possible to get closer to the new target plasma steady state concentrations of E2609 required to achieve the intended target levels of CSF Aβ(1-x) reduction than is possible with the initially planned doses, given the limitation that E2609 dose adjustments will have to be in 5-mg increments or decrements. Subjects already randomized to a dose that needs to be adjusted will be switched to the new adjusted dose and complete their treatment at this new dose.

Once 60 subjects in Stage A have completed at least 12 weeks of treatment (or discontinued study drug early) an interim safety analysis will be conducted by Eisai and the DSMB. (revised per Amendment 01) Subjects in Stage A will continue study drug while the DSMB reviews all the available safety data, but randomization of additional subjects will not take place (ie, recruitment into Stage B will not commence) until the safety analysis is completed by the DSMB.

If there are safety signals with one of the E2609 dose groups that would require dose adjustment, changes to dose will be reflected in an amendment to the protocol. Information on how these subjects will be handled in the primary analysis will be described in the Statistical Analysis Plan.

**Stage B**

Stage B will start after the DSMB safety review of Stage A has shown acceptable safety and tolerability of E2609 and after the doses of E2609 to be used in Stage B are confirmed. Stage B will enroll, randomize, and dose additional eligible subjects up to a maximum of 500 MCI/Prodromal and up to a maximum of 200 mild to moderate AD. The final total number of MCI/Prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. (revised per Amendment 01) Safety data from Stage B will continue to be reviewed by the DSMB (approximately every 3 months) until recruitment to the study is completed; following this the DSMB will meet approximately every 6 months.

In Stage B, both cohorts will include separate placebo groups. The MCI/Prodromal cohort will include 3 doses of E2609 (5 mg, 15 mg, and 50 mg QD) whereas the Mild to Moderate AD cohort will only include 2 doses of E2609 (15 mg and 50 mg QD). (revised per Amendment 01)

Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B. Randomization of MCI/Prodromal subjects into Stage B will commence according to a fixed schedule (1:1:1:1; placebo:5 mg E2609:15 mg E2609:50 mg E2609) until a total of 100 MCI/Prodromal subjects (including those from Stage A) have been randomized. (revised per Amendment 01) The remaining subjects in the MCI/Prodromal cohort in Stage B will then be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. The mild to moderate AD subjects will be randomized according to a fixed schedule (1:1:1 placebo; 15 mg E2609; 50 mg E2609) throughout Stage B. (revised per Amendment 01)

**Early Discontinuation**

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug. Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie, at Visits 11, 14, 15, 16, 17, and 18) if these visits have not already been performed. At these visits, only the clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB and ISLT) will be conducted. Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

**Follow-Up**

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug (Visit 19) and a second 12 weeks after the last dose of study drug (Visit 20). If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the posttreatment Follow-Up period.

**Number of Subjects**

- Stage A: Approximately 250 MCI/Prodromal or mild to moderate AD subjects will be screened to provide 60 randomized subjects (target of 15 subjects per treatment arm). There will be no limit to the number of subjects randomized from either clinical cohort. (revised per Amendment 01)
- Stage B: Up to approximately 2100 MCI/Prodromal subjects will be screened to provide up to 500 randomized subjects. The final number of MCI/Prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. In addition, up to approximately 835 subjects with mild to moderate AD will be screened to provide up to 200 randomized mild to moderate AD subjects. The final number of mild to moderate AD subjects randomized in Stage B will depend upon the number of mild to moderate AD subjects previously randomized during Stage A. (revised per Amendment 01)

**Inclusion Criteria**

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD or AD dementia and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at both Screening and Baseline:**

   a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation
   b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT
   c. FAQ ≤24 (revised per Amendment 01)
   d. MMSE ≥16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading
3. Male or female, age 50 to 85 years, inclusive at time of consent
4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.
5. If receiving acetylcholinesterase inhibitors (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.
6. Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization.

**Exclusion Criteria**

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or magnetic resonance imaging (MRI)
2. Modified Hachinski Ischemic Scale >4

3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and < 1cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could confound the MCI/Prodromal or mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendment 01)
7. A score of ≥8 on the 15-item Geriatric Depression Scale at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the lower limit of normal (LLN) for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
12. Any contraindications to lumbar puncture for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity)
13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.

17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization
20. Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests conducted at Visit 2 (eg, MMSE, CDR) must be repeated.
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below LLN and confirmed by a repeat test conducted 1 week after the initial test
23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the Investigator and the Medical Monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of clinical immunodeficiency. The discussion with the Medical Monitor should include a detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)
24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate electrocardiograms (ECGs). A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute at Screening or Baseline
29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)

31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.
33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with

spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period and for 28 days after study drug discontinuation.

- Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.
- Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
  (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

44. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or not practicing highly effective contraception throughout the study period or for 28 days after study drug discontinuation). No sperm donation is allowed during the study period or for 28 days after study drug discontinuation.

**Study Treatments**

E2609 tablets of 5-mg, 10-mg and 25-mg dose strengths will be supplied. Placebo tablets to match E2609 will be of identical appearance. Each subject will receive 2 tablets, which when combined will make up the required doses of E2609 (see below) or placebo, to be administered orally QD with food.

- Stage A: 3 doses (5 mg, 15 mg, and 50 mg) of E2609 or placebo (revised per Amendment 01)
- Stage B, MCI/Prodromal Cohort: 3 doses (5 mg, 15 mg, and 50 mg) of E2609 or placebo (revised per Amendment 01)
- Stage B, Mild to Moderate AD Cohort: 2 doses (15 mg and 50 mg) of E2609 or placebo. (revised per Amendment 01)

**Duration of Treatment**

The maximum duration of a subject's participation in the study will be approximately 2 years, comprising:

- Screening and Baseline Periods (Prerandomization Phase): up to 60 days

  (In subjects who have an active infection within 4 weeks of the planned randomization date, the duration of the pre-randomization phase can be extended by up to 4 weeks to allow additional time for resolution of the infection.)
- Treatment Period (Randomization Phase): up to 78 weeks
- Follow-Up Period (Randomization Phase): 12 weeks (post last dose)

**Concomitant Drug/Therapy**

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit (see Appendix 2 for a detailed listing of these agents):

- Anticoagulants (eg, warfarin, digabatrin) are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization
- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization

Subjects taking AChEIs or memantine must meet the following criteria in order to be included in the primary analyses:

- On a stable dose for 12 weeks before the baseline cognitive assessments at Visit 2
- Remain on a stable dose while on study

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for the primary analyses.

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if, in the opinion of the investigator, this will not interfere with study procedures or subject safety, and are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks.

**Assessments**

**Efficacy Assessments**

Derived ADCOMS: The derived ADCOMS represents a new approach to the analysis of selected items (12 total) from 3 fully validated and well established clinical tools, the ADAS-cog (4 items), the MMSE (2 items), and the CDR (all 6 items). The 3 scales should be administered in full in the morning, or, if not possible, consistently at the same time of day.

Alzheimer's Disease Assessment Scale - cognitive subscale: The 14-item version will be used since it is considered more relevant for subjects with MCI/Prodromal AD or mild AD.

Mini Mental State Examination: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing.

Clinical Dementia Rating: Assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

CogState Brief Battery: A computer-based battery comprising 4 cognitive tests:

1. Detection – a simple reaction time test. Speed of response is the measure.
2. Identification – a simple choice reaction time test. Speed of response is the measure.
3. One Card Back – a simple working memory test. Accuracy of response is the measure.
4. One Card Learning – a visual learning and memory test. Accuracy of response is the measure.

International Shopping List Task: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall.

Functional Assessment Questionnaire: The FAQ has 10 items concerned with performing daily tasks necessary for independent living. Either a caregiver or informant or the subject provides performance ratings on 10 complex activities of daily living performed within the preceding 4 weeks.

Volumetric Magnetic Resonance Imaging: vMRI will be used to evaluate disease modification, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs.

**Pharmacokinetic Assessments**

Blood and CSF samples will be collected for the determination of the concentrations of E2609. Analyses of metabolite concentrations may be performed depending on emerging data from other studies with E2609.

**Pharmacodynamic, Pharmacogenomic and Other Biomarker Assessments**

Brain atrophy will be measured by vMRI: see Efficacy Assessments (above).

The soluble biomarkers Aβ(1-x), Aβ(1-42), total tau (t-tau), and p-tau will be measured in CSF. BACE1 levels and activity in CSF will also be measured. Other exploratory biomarkers (eg, miRNA) may also be evaluated in plasma and/or CSF.

Amyloid PET imaging will be used to confirm that all subjects eligible for progression to the

Baseline Period have amyloid deposition in the brain. Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted through to the time at which acceptable 18-month PET scans have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used.

Apolipoprotein E (*ApoE*) and *NAT2* genotyping/phenotyping will be conducted. *ApoE4* homozygous or heterozygous status versus non-carriers and *NAT2* status will be used in the statistical analysis to determine the effects on treatment response and safety. Remaining genomic DNA may also be stored for up to 15 years to be used to examine the role of DNA sequence variability on the absorption, distribution, metabolism, and elimination of E2609, development of AEs, as well as the underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single-nucleotide polymorphisms with PK, safety, or PD data.

**Safety Assessments**

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR. (revised per Amendment 01) Routine safety assessments will include the monitoring and recording all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

Complete blood counts and lymphocyte subset absolute counts and percentages will be measured (by a centralized laboratory) every week for the first month, every 2 weeks for the next 2 months (Months 2 and 3) and monthly for the next 3 months (Months 4, 5, and 6). Thereafter they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits. Serum IgG, IgA, and IgM will be monitored monthly for the first 3 months, at 6, 12, and 18 months, and at both Follow-Up Visits.

Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and posttreatment for exploratory immunomodulatory and immune-based analyses.

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at baseline and at 3-month intervals during the Treatment Period. These assessments will specifically include evaluation of any areas of depigmentation or rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregivers/ informants will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so such AEs can be reviewed promptly.

Baseline and on-study blood, DNA, and CSF samples will be taken and stored from all subjects. These samples may be tested for exploratory biomarkers associated with study drug or disease, or in the event that a subject develops AEs that warrant further investigation

(eg, to test if a subject with a treatment-emergent infection was exposed to any suspected infective agents before treatment with study drug).

Safety brain MRI assessments will be performed at Screening, at 6, 12, and 18 months during the Treatment Period and at the final Follow-Up Visit. Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Full neurological examinations will be performed at Baseline, at 6, 12, and 18 months, and at both Follow-Up Visits, by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations. The neurological examinations will include muscle strength testing and assessment of cranial nerves including olfaction as well as other parts of the CNS.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments will include the ADAS-$cog_{14}$, MMSE, and CBB.

An assessment of suicidality using the C-SSRS will be performed at Screening and Baseline and at regular intervals throughout the Treatment and Follow-Up Periods.

An ophthalmic examination (including retinal examination) will be conducted at Baseline. An additional examination will be conducted if the subject experiences visual disturbances during the course of the study.

A number of safety-related criteria for discontinuation of study drug are specified for the study.

**Bioanalytical Methods**

Plasma and CSF concentrations of E2609 will be measured by a validated liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) in both CSF and plasma will be measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and post-screening analysis of CSF Aβ(1-42), tau, and p-tau will be performed using ELISAs.

BACE1 levels and activity may be measured using a customized assay. Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

**Statistical Methods**

All statistical tests will be based on the 5% (2-sided) level of significance, except for the Bayesian methods on the primary endpoint.

**Study Endpoints**

**Primary Endpoint**

- Change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects

**Secondary Endpoints**

Change from baseline in:

- Total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- CSF Aβ(1-x) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
- The derived ADCOMS at 18 months of treatment in mild to moderate AD subjects (revised per Amendment 01)

**Exploratory Endpoints**

(revised per Amendment 01)

Change from baseline in:

- The derived ADCOMS at 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
- Total hippocampal volume at 12 and 18 months of treatment in mild to moderate AD subjects as measured by vMRI
- CSF Aβ(1-42) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
- CSF Aβ(1-x) and Aβ(1-42) after 4 weeks and 18 months of treatment in mild to moderate AD subjects
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ in MCI/Prodromal and mild to moderate AD subjects
- CSF biomarkers of neurodegeneration (eg, tau and p-tau) at 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects
- Plasma and CSF amyloid, and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild to moderate AD subjects
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and, 18 months in MCI/Prodromal and mild to moderate AD subjects as measured by vMRI
- Brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- The population PK parameters of E2609 including the effect of intrinsic and extrinsic factors (including *NAT2* phenotype) in MCI/Prodromal and mild to moderate AD subjects

**Analysis Sets**

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.

- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set is the subset of subjects in the FAS who sufficiently comply with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

**Efficacy Analyses**

***The MCI/Prodromal cohort:*** This study in the MCI/Prodromal cohort is based on Bayesian adaptive design. Frequent interim analyses will be performed to assess the probability of early success and futility and to make early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis. Key definitions relevant to the Bayesian aspects of the adaptive design are given below.

**Study Definitions**

- **Maximum Effective Dose ($d_{Max}$):** The dose that achieves the greatest treatment effect.
- **$ED_{90}$:** The lowest dose that achieves at least 90% of the $d_{Max}$ treatment effect in the derived ADCOMS.
- **Early Success:** The study in the MCI/Prodromal cohort will meet early success criteria if the probability that the $ED_{90}$ at 18 months of treatment achieves 25% improvement over placebo is at least 80%. Early success is achieved before all MCI/Prodromal subjects complete 18 months of treatment and can only be determined after at least 200 MCI/Prodromal subjects have been randomized. If early success is declared before full randomization, the randomization of new MCI/Prodromal subjects will stop but subjects already randomized into the study will receive the full 18 months of treatment (following confirmation from the Sponsor's Senior Management).
- **Futility:** The study in the MCI/Prodromal cohort will meet statistical futility criteria if the probability that the $ED_{90}$ is better than placebo by the clinically significant difference of 25% is less than 5% at 18 months of treatment. The statistical futility boundary is binding; if the statistical futility boundary is crossed the study will be considered to have failed.
- **Study Success:** The study in the MCI/Prodromal cohort will be considered a success if an $ED_{90}$ at 18 months treatment has at least an 80% probability of achieving 25% improvement over placebo at either an interim analysis or at the final analysis.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)***:*** All mild to moderate AD subjects will be included in the efficacy evaluations of the Mild to Moderate AD cohort. The analysis of the Mild to Moderate AD cohort is based on the group sequential design. Interim analyses in the Mild to Moderate AD cohort will only be performed after the

MCI/Prodromal cohort crosses the early success boundary. The early efficacy signal based on the change from baseline of ADCOMS at 18 months is defined as crossing the interim-analysis boundaries for overwhelming efficacy in the mild to moderate AD population. The O'Brien-Fleming (OF) boundaries based on Lan-DeMets alpha spending function will be used to assess overwhelming efficacy. The corresponding OF boundaries based on *P* values will be 0.076, 0.0221, and 0.0423 for the first, second, and final analyses, respectively, according to 2 planned interim analyses at the 60% and 80% information fraction. (revised per Amendment 01)

**Analysis for the primary endpoint**

***Primary analysis of primary endpoint***

The primary analysis will be based on MCI/Prodromal subjects from the FAS with the prespecified censoring rule applied. The primary endpoint is the change from baseline to 18 months in the derived ADCOMS. The dose-response of the primary endpoint is modelled with a first-order normal dynamic linear model, where Normal and Inverse-Gamma priors are used. The primary efficacy analysis will calculate the Bayesian posterior probability that the dose identified is the most likely $ED_{90}$ dose that achieves 25% improvement over the placebo arm. At each interim analysis and the final analysis, 2 Bayesian probabilities will be summarized for each active dose: the probability it is the $ED_{90}$ dose and the probability of achieving 25% improvement over the placebo arm.

For the clinical efficacy data (ie, derived ADCOMS, MMSE, ADAS-cog, CDR, CBB, ISLT, and FAQ), subjects will be censored at the time of initiation of treatment with AChEIs or memantine, if they were not on these medications at the time of Baseline cognitive assessment (Visit 2), and will be censored at the time of dose adjustment of AChEIs or memantine if they were already on stable treatment with these medications at the time of Baseline cognitive assessment (Visit 2). The value of the primary endpoint for censored subjects will be imputed using data up to the censoring time and Bayesian longitudinal modeling.

***Sensitivity analyses of primary endpoint***

After unblinding, the primary endpoint will be analyzed using the Bayesian methods described above as well as conventional statistical methods. The following additional Bayesian analyses will be conducted as sensitivity analyses:

- The primary endpoint will be analyzed regardless of initiation of treatment, or dose adjustment, with AChEIs or memantine using the same Bayesian analysis method as primary analysis. This is an intent-to-treat analysis without any censoring.
- In case of early success, the primary analysis as well as the above sensitivity analyses will be repeated after all subjects have completed 18 months of treatment or have been lost to follow-up.

Statistical methods for the final conventional analyses will use a mixed-effects model with repeated measures (MMRM) on the change from baseline in the derived ADCOMS at 18 months. The model will include treatment groups, randomization stratification variables (the presence or absence of ongoing treatment with AChEIs or memantine or both, and *ApoE4* status), and baseline ADCOMS as covariates. Other covariates such as adjusted

hippocampal volume will be studied. These analyses will be performed as sensitivity analyses on the FAS as well as the per protocol set, and as such, no multiplicity adjustments will be made to account for the interim analyses. In case of early success, the conventional analyses will also be performed using the data collected before the interim analysis.

**Analysis for the secondary endpoints**

***The MCI/Prodromal Cohort***

An MMRM will be used to analyze the following secondary endpoints:

- Change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-x) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects. Data from early discontinuations will also be included.

Comparisons between each treatment group and placebo will be performed.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

An MMRM will be used to analyze the change from baseline of derived ADCOMS at 18 months in mild to moderate AD. If there is no treatment group-by-population interaction in the overall study, the MMRM analysis will include all subjects (MCI/Prodromal or mild to moderate AD) in the overall study. Otherwise, the MMRM analysis will only include subjects in the Mild to Moderate AD cohort. The comparison between placebo and active doses will be performed within mild to moderate AD subjects regardless of subjects included in the MMRM analysis. Dunnett's method will be used to control for multiplicity due to multiple comparisons. (revised per Amendment 01)

**Analysis for exploratory endpoints**

(revised per Amendment 01)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in the derived ADCOMS at 12 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in total hippocampal atrophy at 12 and 18 months in mild to moderate AD subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-42) after 4 weeks and 18 months in MCI/Prodromal subjects. Data from early discontinuations will also be included.
- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) after 4 weeks and 18 months in mild to moderate AD subjects. Data from early discontinuations will also be included.
- Change from baseline in the clinical assessments: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in plasma and CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild to moderate AD subjects

- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and 18 months as measured by vMRI in MCI/Prodromal and mild to moderate AD subjects

A linear mixed-model will be used to analyze the following exploratory endpoints:

- Change from baseline in brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in CSF biomarkers of neurodegeneration (eg, tau, p-tau) at 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects

Data from early discontinuations will also be used as appropriate. Comparisons between each treatment group and placebo will be performed.

A linear mixed-model with repeated measures will be used to determine the relationship between the following endpoints:

- Change from baseline in the derived ADCOMS score and the change from baseline in biomarkers in CSF at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in the derived ADCOMS score and change from baseline in imaging biomarkers (hippocampal, whole brain, and total ventricular volumes) at 12 and 18 months in MCI/Prodromal and mild to moderate AD subjects

*ApoE* status for heterozygous and homozygous E4 carriers will be included in the model to assess the effect of *ApoE* status in this relationship.

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). CSF Aβ(1-x), Aβ(1-42), t-tau, p-tau, and BACE1 will be assessed and data will be presented graphically. Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status. Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels and exposure to E2609 in plasma and CSF will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. Additionally, the relationship between CSF exposure to E2609 and the derived ADCOMS at 18 months, and the relationship between CSF exposure to E2609 and the change from baseline for 18 months in the ADAS-cog, the CDR, and the MMSE will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling.

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. Further information is in the "Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments" section. Details of pharmacogenomic testing may be provided and reported separately.

**Safety Analyses**

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, and vital sign measurements will be summarized by treatment group using descriptive statistics.

Lymphocyte Subsets

Lymphocyte subsets (ie, CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages]) and regulatory T cells will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose. Serum IgG, IgM, IgA will be measured and summarized in the same manner as other laboratory parameters.

**Interim Analyses**

An interim safety analysis will be conducted when the first 60 subjects have completed 12 weeks of treatment (or discontinue study drug early) in Stage A. (revised per Amendment 01)

***The MCI/Prodromal Cohort***

Oversight of the Bayesian interim analyses and response adaptive randomization will be conducted by an independent committee that has expertise with Bayesian adaptive design in clinical studies. An unblinded external independent analysis group will provide the interim analysis outcomes to the committee at each interim analysis. The committee will ensure the integrity of the interim analysis and response adaptive randomization process through review of efficacy data. In addition, the committee will act in an independent advisory capacity to monitor the Bayesian interim analysis outcomes according to the early success and futility boundaries prespecified in the protocol. The committee will not be charged with any subject safety issues; this will remain the responsibility of the DSMB. The DSMB will continue to monitor the safety aspects of the study throughout Stage A and Stage B. The study may be stopped for safety at any time.

The first Bayesian adaptive interim analysis will be conducted when 100 MCI/Prodromal subjects have been randomized into the study (ie, including MCI/Prodromal subjects from both Stage A and Stage B). (revised per Amendment 01) Further interim efficacy analyses will be conducted after each additional 50 MCI/Prodromal subjects have been randomized, up to a maximum of 500 MCI/Prodromal subjects (ie, at 100, 150, 200, 250, 300, 350, 400, 450, 500 subjects randomized). If the study reaches full randomization, additional interim analyses will be conducted every 3 months until all subjects complete 18 months of treatment. The study will be monitored for futility at each interim analysis. Starting at the 200 subjects' interim analysis, the study will be monitored for success at each interim analysis. Each interim analysis will be conducted on data for the derived ADCOMS.

If the predefined early success criteria are met during the recruitment period, further recruitment and enrollment of MCI/Prodromal subjects into the study will stop (following confirmation from the Sponsor's Senior Management) and all currently randomized subjects will complete the full 18 months of treatment. No further interim analyses will be conducted after achieving early success.

If the predefined threshold for futility is reached, no additional subjects will be randomized into the study and the treatment of subjects already randomized into the study will stop and the study will be declared as "failed". All subjects will be monitored for safety for 3 months following their last dose.

If neither early success nor futility is reached and the study reaches full randomization, all subjects will complete 18 months of treatment. Interim efficacy analyses will be conducted every 3 months after full randomization is reached to assess futility and early success until all subjects complete 18 months of treatment. After full randomization, all study subjects will stop treatment only in the event of futility.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

A group sequential design will be used for the Mild to Moderate AD cohort. This design includes 3 looks, 2 interim looks (when 60% and 80% information fractions are achieved) and 1 final look. Interim analyses will be performed after the MCI/Prodromal cohort crosses the early success boundary. The corresponding efficacy boundaries will be 0.076, 0.022, and 0.0423 for the first, second, and final analyses, respectively. If the actual information fraction during the interim analyses is different from 60% or 80% at the interim, the efficacy boundaries will be adjusted based on the actual information fraction. If early success in the MCI/Prodromal cohort is not achieved before the final analysis that is performed when all subjects have completed 18 months treatment, then only a final analysis will be performed in mild to moderate AD subjects. In the event of futility in the MCI/Prodromal cohort, an analysis will be performed for the Mild to Moderate AD cohort based on the data for mild to moderate AD subjects available at that time. (revised per Amendment 01)

**Adaptive Randomization in the MCI/Prodromal Cohort**

Randomization to placebo or 1 of 3 dose groups of E2609 will be fixed for the first 100 MCI/Prodromal subjects randomized in the study (1:1:1:1; placebo to each of the 3 active doses for the first 100 MCI/Prodromal subjects randomized, including those randomized from both Stage A and Stage B). Thereafter, randomization probabilities to each treatment group will be updated at each interim analysis, such that the randomization probability will be increased for the placebo group and dosage groups that represent the potential target dose ($ED_{90}$), and simultaneously decreased for other active arms. (revised per Amendment 01)

**Randomization in the Mild to Moderate AD Cohort** (revised per Amendment 01)

In Stage A, the mild to moderate AD subjects will be randomized to placebo or 1 of 3 E2609 dose groups (5 mg, 15 mg, and 50 mg of E2609) at a 1:1:1:1 ratio, while in Stage B, the mild to moderate AD subjects will be randomized to placebo or 1 of 2 E2609 dose groups (15 mg and 50 mg E2609) at a 1:1:1 ratio. (revised per Amendment 01)

**Stratification** (revised per Amendment 01)

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

**Sample Size Rationale**

***Sample Size Rationale in the MCI/Prodromal cohort***

Primary endpoint – derived ADCOMS: The sample size and design characteristics to test the hypothesis for the primary objective based on the primary endpoint were determined by means of simulations. Extensive study simulations have shown that a total of 500 subjects will be sufficient to demonstrate that the most likely $ED_{90}$ dose achieves a 25% improvement over placebo with a probability of at least 80% in the interim and final analyses. There is at least a 90% probability of study success for the dose response scenarios where treatment was considered to have a clinically meaningful treatment effect. Simulations have also shown that if there is no obvious dose effect, the probability of falsely claiming superiority to placebo is at most 5%.

For each of the 4 treatment groups (3 active doses and placebo), the final number of subjects per group will differ depending on the observed interim treatment responses.

vMRI: The null hypothesis is that there is no difference between active dose and placebo. There are 3 null hypotheses corresponding to 3 active doses. The alternative hypothesis is that at least 1 null hypothesis is false (1-sided). The null hypotheses will be tested using Dunnett's method with 1-sided alpha of 0.05. The statistical power was estimated through simulation for a moderate dose-response assumption that the percent reduction in change from baseline of total hippocampal volume compared with placebo would be 15%, 20%, and 25% corresponding to the 3 doses, respectively. The estimated power for actual planned study sample size is 78% at 18 months assuming an attrition rate of 20% at 18 months. Under a stronger dose-response assumption (ie, the percent reduction in change from baseline of total hippocampal volume compared with placebo is twice as much as that in the moderate dose-response assumption), the estimated power is at least 99% at 18 months.

Amyloid PET: The null and alternative hypotheses and statistical test are the same as those for vMRI. To estimate the sample size for the amyloid PET imaging subgroup at 18 months, a common SD of change from baseline was estimated at 0.33 and a reasonable mean difference between treatment and placebo was estimated as 0.25 (standardized uptake value ratio [SUVR]). Assuming a moderate dose-response, the best dose would achieve a difference of 0.25 (SUVR) and the middle and low doses would achieve a difference of 0.2 and 0.15 (SUVR), respectively, it would require a total of 100 subjects from all 4 arms at 18 months to achieve 80% power.

***Sample Size Rationale for the Mild to Moderate AD Cohort*** (revised per Amendment 01)

ADCOMS at Month 18: The null hypothesis is that there is no difference between active dose and placebo. There are 2 null hypotheses corresponding to 2 active doses. The alternative hypothesis is that at least 1 null hypothesis is false. The null hypotheses will be tested using Dunnett's test with 2-sided alpha of 0.05 as described for the Mild to Moderate

AD cohort in the secondary analysis section. The statistical power was estimated through simulation for the dose-response assumption that the percent reduction in change from baseline of ADCOMS at 18 months compared with placebo would be 33% and 50% corresponding to the 2 doses, respectively. The estimated power for the actual planned 200 mild to moderate AD subjects is approximately 80% assuming a 2-sided alpha of 0.05. (revised per Amendment 01)

# 3 TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES



## LIST OF IN-TEXT FIGURES



## LIST OF APPENDICES

# 4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| Aβ | amyloid β |
| Aβ(1-x) | amyloid β (1-x) (ie, the amyloid β monomer from amino acid 1 to x [eg 1-42]) |
| AChEI | Acetylcholinesterase inhibitor |
| AD | Alzheimer's disease |
| ADAS-cog | Alzheimer's Disease Assessment Scale - cognitive subscale |
| ADCOMS | Alzheimer's Disease Composite Score |
| AE | Adverse Event |
| ApoE | Apolipoprotein E |
| AUC | area under the concentration x time curve |
| $AUC_{(0\text{-}24h)ss}$ | area under the concentration x time curve at steady state from time zero to 24 hours |
| BACE1 | Beta-amyloid converting enzyme 1 |
| BP | blood pressure |
| bpm | beats per minute |
| CBB | CogState Brief Battery |
| CBP | childbearing potential |
| CDR | Clinical Dementia Rating |
| CES2 | carobxyesterase-2 |
| CFR | Code of Federal Regulations |
| $C_{max,ss}$ | maximum plasma concentration at steady state |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| CRA | clinical research associate |
| CRF | case report form |
| CRO | contract research organization |
| CSF | cerebrospinal fluid |
| $C_{ss,av}$ | average steady-state concentration |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CTA | Clinical Trial Agreement |
| CYP | cytochrome P450 |
| $d_{Max}$ | Maximum effective dose |
| DSMB | data safety monitoring board |
| ECG | electrocardiogram |
| eCRF | electronic case report form |

| Abbreviation | Term |
|---|---|
| ED | early discontinuation |
| $ED_{90}$ | lowest effective dose that achieves 90% of the greatest treatment effect |
| ELISA | enzyme-linked immunosorbent assay |
| FAQ | Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire) |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FLAIR | fluid-attenuated inversion recovery |
| GCP | Good Clinical Practice |
| GDS | Geriatric Depression Scale |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |
| HCVAb | hepatitis C virus antibody |
| HSV | herpes simplex virus |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ID | identifier |
| IEC | Independent Ethics Committee |
| Ig | immunoglobulin (eg, IgA, IgG, IgM) |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISLT | International Shopping List Task |
| IxRS | interactive voice and web response system |
| LLN | lower limit of normal |
| LNH | low/normal/high |
| LP | lumbar puncture |
| MAD | multiple ascending dose |
| MCI | mild cognitive impairment |
| MCI/Prodromal | Mild Cognitive Impairment due to Alzheimer's Disease/ Prodromal Alzheimer's Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mild to moderate AD | mild to moderate dementia due to Alzheimer's Disease |
| miRNA | micro-ribonucleic acid |
| MMRM | mixed-effects model with repeated measures |
| MMSE | Mini Mental State Examination |

| Abbreviation | Term |
|---|---|
| MRI | magnetic resonance imaging |
| NAT2 | N-acetyltransferase 2 |
| NIA-AA | National Institute on Aging-Alzheimer's Association |
| OF | O'Brien-Fleming |
| PBMC | peripheral blood mononuclear cell |
| PD | Pharmacodynamic(s) |
| PET | positron emission tomography |
| PGx | pharmacogenomic(s) |
| PK | pharmacokinetic(s) |
| PP | per protocol |
| PRN | Pro re nata |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| p-tau | phosphorylated-tau |
| QD | once daily |
| QTc | corrected QT interval |
| QTcF | QTc interval calculated using Fridericia's formula |
| R | randomization |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reaction |
| SUVR | standardized uptake value ratio |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |
| TEMAV | treatment-emergent markedly abnormal laboratory values |
| t-tau | total tau |
| ULN | upper limit of normal |
| UNS | unscheduled |
| vMRI | volumetric magnetic resonance imaging |
| WHO DD | World Health Organization Drug Dictionary |
| β-hCG | beta-human chorionic gonadotropin |

# 5 ETHICS

## 5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA][s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigators or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

## 5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (CFR) (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

- European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved European Union member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

## 5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject and the identified caregiver or informant, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or understand it or if the identified caregiver or informant is unable to read, an impartial witness should be present during the entire informed consent discussion. If, in the Investigator's opinion, a subject lacks capacity to consent, the subject's assent should be obtained in addition to the written informed consent of a legal representative (capacity to consent and definition of legal representative should be determined in accordance with applicable local laws and regulations). (revised per Amendment 01) After the ICF and any other written information to be provided to subjects is read and explained to the subject and the identified caregiver or informant, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified caregiver or informant should also consent to supporting the subject's participation in the study and will be provided with a separate written ICF for his or her participation in the study, to be signed before he or she participates in any further aspects of the study.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified caregiver or informant must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified caregiver or informant will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified caregiver or informant should be

informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

# 6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 125 investigational sites globally (30 sites in the United States for Stage A and 125 sites globally for Stage B). (revised per Amendment 01)

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

# 7 INTRODUCTION

At this time, there is no cure for Alzheimer's disease (AD), no known way of slowing down the progression of this disease, and no approved treatment available to reverse the deterioration. There is, therefore, an urgent unmet medical need for drugs that slow or prevent disease progression. Beta-amyloid converting enzyme 1 (BACE1) is a key enzyme responsible for the production of amyloid β (Aβ) peptides and plaque formation, and several reports have described elevated levels of BACE1 in AD brains (Coulson, et al., 2010, Lu, et al., 2012). Once amyloid plaques form, Aβ causes BACE1 levels to increase further, thus accelerating Aβ generation and plaque growth via a positive feedback loop. Therefore, BACE1 is a promising target for modifying or treating AD.

It is now widely accepted that mild cognitive impairment (MCI) due to AD and mild to moderate AD dementia are stages on a single disease spectrum, which follows an Alzheimer's pathological cascade. (revised per Amendment 01) Recent consensus papers from the international workgroups of the National Institute on Aging-Alzheimer's Association (NIA-AA), have endorsed this hypothesis (Albert, et al., 2011; Jack, et al., 2011; McKhann, et al., 2011; Sperling, et al., 2011).

From a clinical standpoint, demonstration of an effect on slowing disease course is hampered by the lack of sensitive tools for detecting relatively small changes in progression or treatment effect especially in early disease. In addition, drugs that are expected to slow disease progression require longer study durations to ensure adequate separation from placebo. These challenges have resulted in the use of biomarkers as surrogates for clinical effect in Phase 2 studies, in order to facilitate the development process for disease modifying agents. However, subsequent Phase 3 AD studies based solely on biomarker findings in Phase 2 have failed to show clinical effect, due, in part, to the fact that biomarkers may not predict clinical outcomes for potential disease modifying agents. These findings underscore the need for innovative approaches to clinical study design for measuring the effect of treatment.

E2609 is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, E2609 inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in cerebrospinal fluid (CSF) and plasma (rat, guinea pig, and monkey). In humans, E2609 has been shown to inhibit BACE1 enzyme activity in CSF and lower the levels of Aβ, including amyloid beta monomer from amino acid 1 to x (Aβ[1-x]), Aβ(1-40) and Aβ(1-42), in CSF both in vitro and in vivo. See the Investigator's Brochure for additional information. The target indication for E2609 is therefore treatment and disease modification of AD.

The present clinical study represents the sole Phase 2 study for the E2609 program, and is designed to establish Proof of Concept in subjects with Mild Cognitive Impairment due to Alzheimer's Disease/Prodromal Alzheimer's Disease (referred to as MCI/Prodromal throughout the protocol). The study also allows investigation of efficacy in subjects with mild to moderate dementia due to Alzheimer's Disease (referred to as mild to moderate AD throughout the protocol) to determine whether the effects of E2609 in this later stage population are comparable with those established in the MCI/Prodromal population within

this same study. (revised per Amendment 01) In the MCI/Prodromal population, Bayesian response adaptive randomization design is used with frequent interim analyses to continually update randomization allocation based on emerging clinical endpoint data. This approach allows for ongoing assessment of drug futility or evidence of early success and can mitigate the risks associated with larger and longer studies required to demonstrate clinical efficacy by leading to more efficient study termination or early advancement to a Phase 3 program. Results from this study will guide both the decision to move into Phase 3 development and the selection of the dose strengths to be taken into Phase 3. Moreover, this study is intended to be supportive for registration in the MCI/Prodromal population.

In the MCI/Prodromal population, this study will compare placebo and 3 oral doses of E2609 (5 mg, 15 mg and 50 mg) administered once daily (QD) for 18 months. In the mild to moderate AD population, this study will compare placebo and 2 oral doses of E2609 (15 mg and 50 mg) administered QD for 18 months. To date, the longest duration of dosing with E2609 is 14 days (multiple ascending dose [MAD] Study E2609-A001-002 [Study 002]). (revised per Amendment 01)

This study (E2609-G000-202 [Study 202]) will comprise 2 stages: Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 in the United States sites only, before expanding enrollment to a larger and more global population of subjects in Stage B. This design will allow close monitoring of safety by an independent data safety monitoring board (DSMB), including a formal safety review as soon as the first 60 randomized subjects have completed 12 weeks of treatment, have discontinued study drug or have withdrawn from the study. The study also includes a number of exclusion criteria, specific blinded safety monitoring procedures and safety criteria for discontinuation of study drug in light of the preclinical and clinical safety data collected to date following administration of E2609.

## 7.1 Nonclinical and Clinical Safety Data

The toxicity of E2609 has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomologus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by E2609 in a clinical setting. Further details of the nonclinical data to date with E2609 can be found in the Investigator's Brochure.

The clinical program to date includes 6 Phase 1 studies:

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, single ascending dose (SAD) study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled MAD study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the pharmacokinetic (PK) levels of E2609 and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of E2609. It also investigated the effects of E2609 on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [$^{14}$C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of E2609 under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) was a randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with E2609. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with E2609. In elderly subjects treated with 50 mg of E2609, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTc interval calculated using Fridericia's formula (QTcF) from baseline (14.9 msec at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of E2609 might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that E2609 altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of E2609. A single dose of E2609 up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, E2609 administered at doses of 200 and 400 mg was associated with

reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of E2609 on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP3A4] and carboxyesterase-2 [CES2]) increased by approximately 70% the area under the concentration × time curve (AUC) of E2609. Consequently, strong inhibitors of CY3A4 will be prohibited in this study.

Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of E2609. Therefore, no restrictions are required for the use of concomitant medications which are known to be inducers of CYP450 enzymes. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of E2609 when coadministered with E2609 but not when dosed at least 2 hours apart from E2609. E2609 (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of E2609. Therefore, on the basis of drug interaction considerations, the only restriction of concomitant medications is that for strong inhibitors of CYP3A4.

# 8 STUDY OBJECTIVES

## 8.1 Primary Objectives

The primary objectives are:

1. To evaluate the efficacy of daily dosing with 3 doses of E2609 compared with placebo by establishing the lowest effective dose that achieves 90% of the greatest treatment effect ($ED_{90}$) for E2609 on the derived Alzheimer's Disease Composite Score (ADCOMS) at 18 months of treatment in subjects with MCI/Prodromal
2. To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with mild to moderate AD (revised per Amendment 01)

## 8.2 Secondary Objectives

The secondary objectives are:

1. To evaluate the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects, as measured by volumetric magnetic resonance imaging (vMRI)
2. To evaluate the effect of E2609 compared with placebo on Aβ(1-x) in CSF after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
3. To evaluate the efficacy of E2609 compared with placebo on the derived ADCOMS at 18 months in mild to moderate AD subjects (revised per Amendment 01)

## 8.3 Exploratory Objectives

(revised per Amendment 01)

The exploratory objectives are:

1. To explore the effect of E2609 compared with placebo on the derived ADCOMS following 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
2. To explore the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in mild to moderate AD subjects, as measured by vMRI
3. To explore the effects of E2609 compared with placebo on Aβ(1-42) in CSF after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
4. To explore the effects of E2609 compared with placebo on Aβ(1-x) and Aβ (1-42) in CSF after 4 weeks and 18 months of treatment in mild to moderate AD subjects

5. To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during posttreatment follow-up, in MCI/Prodromal and mild to moderate AD subjects, by assessment of:
   a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
   b. The Clinical Dementia Rating (CDR) scale
   c. The Mini-Mental State Examination (MMSE)
   d. The CogState Brief Battery (CBB)
   e. The Functional Assessment Questionnaire (FAQ; (also known as the Functional Activities Questionnaire)
   f. The International Shopping List Task (ISLT)
6. To explore the effects of E2609 compared with placebo on various biomarkers in MCI/Prodromal and mild to moderate AD subjects. Biomarkers to be explored include:
   a. CSF biomarkers of neurodegeneration (eg, tau, phosphorylated-tau [p-tau]) after 18 months of treatment
   b. Plasma and CSF amyloid, and CSF BACE1 measurements during 18 months of treatment and during posttreatment follow-up
   c. vMRI measurements including left and right hippocampal volume, whole brain volume, and total ventricular volume at 6, 12, and 18 months of treatment and during posttreatment follow-up
   d. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)
7. To characterize the population PK of E2609 in MCI/Prodromal and mild to moderate AD subjects, and to examine the effect of intrinsic and extrinsic factors (including N-acetyltransferase 2 [*NAT2*] phenotype) on the PK
8. To explore the relationship between the treatment effects of E2609 on the ADCOMS and its effects on CSF amyloid, CSF BACE1, CSF tau, and vMRI in MCI/Prodromal and mild to moderate AD subjects

# 9 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan

Study 202 is a multicenter placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild to moderate AD. (revised per Amendment 01)

A common set of inclusion criteria, consistent with the NIA-AA clinical research criteria for MCI due to AD or mild to moderate AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild to moderate AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria. (revised per Amendment 01)

The study will be conducted in 2 stages, Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 (at least 12 weeks) before expanding enrollment to include a larger number of subjects in Stage B. . All MCI/Prodromal subjects will be included in the primary efficacy evaluation irrespective of whether they were recruited into Stage A or Stage B. Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B. All mild to moderate AD subjects will be included in the efficacy evaluation of that cohort. (revised per Amendment 01)

Both Stage A and Stage B will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days) will consist of a Screening Visit and a Baseline Visit. Screening assessments will be organized into 4 tiers; see Section 9.5.2.2, Table 6, and Figure 2.

All screening assessments must be completed, and eligibility to continue to the Baseline Period confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

In Stage A, all subjects (MCI/Prodromal and mild to moderate AD) will be randomized 1:1:1:1 to 4 treatment groups (E2609 at 3 doses or placebo). In Stage B, randomization of MCI/Prodromal subjects will start off at a 1:1:1:1 ratio (E2609 at 3 doses or placebo), until a total of 100 MCI/Prodromal subjects have been randomized. Remaining subjects in the MCI/Prodromal cohort will be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. Subjects with mild to moderate AD who are recruited in Stage B will be randomized in a 1:1:1 ratio to 3 treatment groups (E2609 at 2 doses or placebo). (revised per Amendment 01)

An overview of the study design is presented in Figure 1.

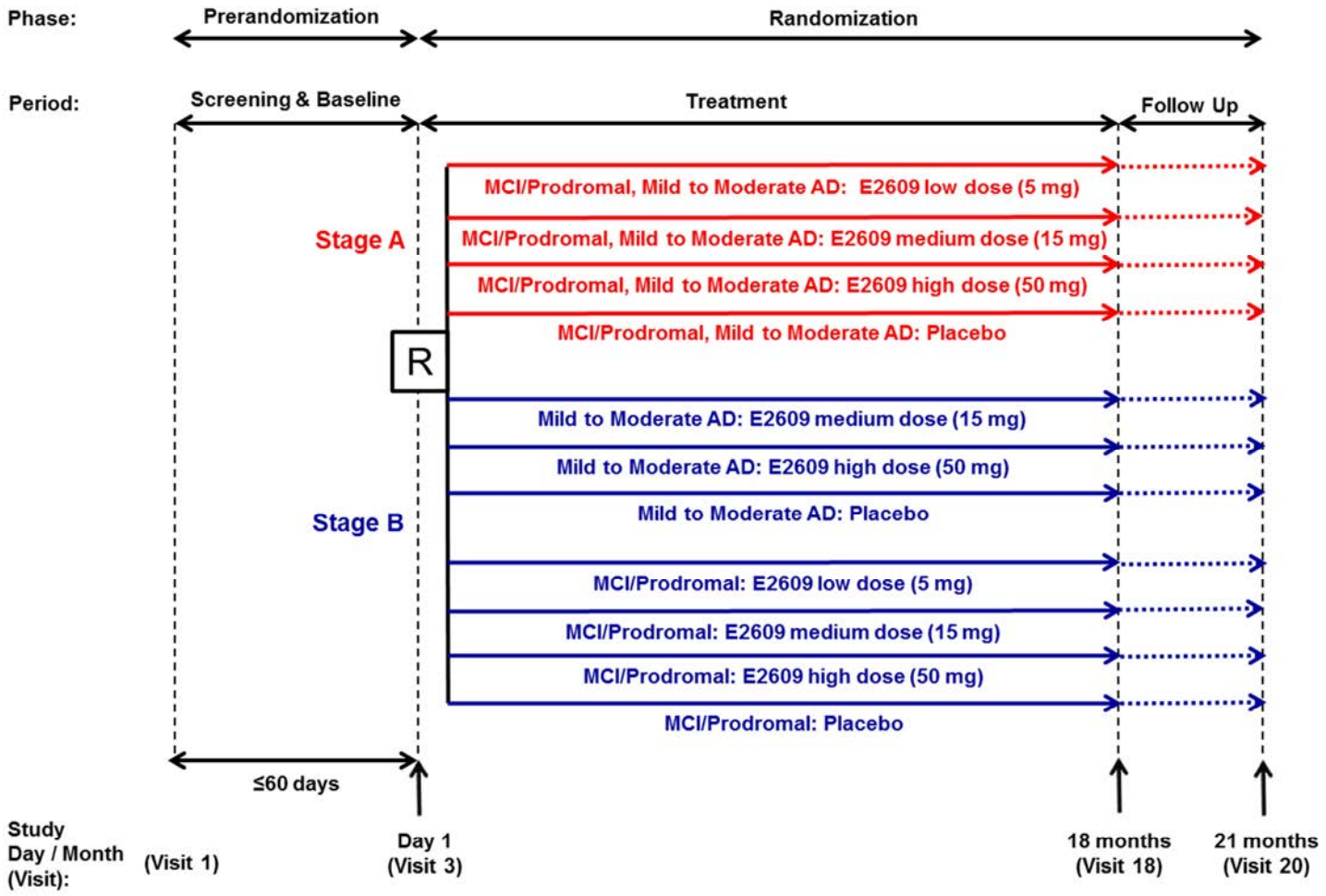



**Figure 1 Design of Study E2609-G000-202**

(revised per Amendment 01 )

R = randomization.

**Stage A**

Stage A will be limited to approximately 30 sites in the United States. (revised per Amendment 01) Stage A will randomize 60 eligible subjects at Visit 3, 1:1:1:1 to 4 treatment groups within each clinical cohort. (revised per Amendment 01) There will be no Bayesian adaptation during Stage A. In addition to the placebo group, 3 doses of E2609 will be used to reduce CSF Aβ levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/PD modeling shows these doses should achieve these targets when administered QD with food and will be confirmed or adjusted based on the 4-week assessment of CSF Aβ(1-x) (see Section 9.4.4).

During Stage A, safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the first subject is randomized during Stage A, an independent DSMB (including at least 1 immunologist) will review all safety data in an unblinded manner. The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. Unless the DSMB recommends otherwise, randomization of subjects into Stage A will continue until 60 subjects have been randomized and dosed. (revised per Amendment 01)

After 60 subjects in Stage A have completed 4 weeks of treatment, an interim analysis of the E2609 PK and PD profiles will be used to confirm the E2609 doses to be used for Stage B (see Section 9.4.4). (revised per Amendment 01)

Once 60 subjects in Stage A have completed at least 12 weeks of treatment (or discontinued study drug early) an interim safety analysis will be conducted by Eisai and the DSMB. (revised per Amendment 01) Subjects in Stage A will continue study drug while the DSMB reviews all the available safety data, but randomization of additional subjects will not take place (ie, recruitment into Stage B will not commence) until the safety analysis is completed by the DSMB. At the time of this interim safety analysis, some subjects will have more than 12 weeks of safety data.

If there are safety signals with one of the E2609 dose groups that would require dose adjustment, changes to dose will be reflected in an amendment to the protocol. Information on how these subjects will be handled in the primary analysis will be described in the Statistical Analysis Plan.

**Stage B**

Stage B will start after the DSMB safety review of Stage A has shown acceptable safety and tolerability of E2609 and after the doses of E2609 to be used in Stage B are confirmed. Based on data from Stage A, the protocol will be reviewed and may be amended before beginning Stage B. Safety data from Stage B will continue to be reviewed by the DSMB (approximately every 3 months) until recruitment in the study is completed; following this the DSMB will meet approximately every 6 months.

Stage B will be conducted globally and will enroll, randomize, and dose additional eligible subjects up to a maximum of 500 MCI/Prodromal subjects and up to a maximum of 200 mild

to moderate AD subjects. The final total number of MCI/Prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. (revised per Amendment 01)

In Stage B, both cohorts will include separate placebo groups. The MCI/Prodromal cohort will include 3 doses of E2609 (5 mg, 15 mg, and 50 mg QD), whereas the Mild to Moderate AD cohort will only include 2 doses of E2609 (15 mg and 50 mg QD). (revised per Amendment 01)

Bayesian response adaptive randomization will be used in the MCI/Prodromal cohort during Stage B. Randomization of MCI/Prodromal subjects into Stage B will commence according to a fixed schedule (1:1:1:1; placebo:5 mg E2609:15 mg E2609:50 mg E2609) until a total of 100 MCI/Prodromal subjects (including those from Stage A) have been randomized. (revised per Amendment 01) The remaining subjects in the MCI/Prodromal cohort in Stage B will then be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. The mild to moderate AD subjects will be randomized according to a fixed schedule (1:1:1 placebo; 15 mg E2609; 50 mg E2609) throughout Stage B. (revised per Amendment 01)

Interim efficacy analyses are planned and are discussed in Section 9.7.3.

### 9.1.1 Prerandomization Phase

The Prerandomization Phase includes a Screening Visit and a Baseline Visit. All Screening Visit assessments must be completed and eligibility to progress must be confirmed before any Baseline Visit assessments are performed. All Screening Visit and Baseline Visit assessments must be completed within 50 days and a window of 7 to 10 days is to be observed between the completion of all Baseline Visit assessments and randomization into the study at Visit 3. Thus, the Prerandomization Phase will last for up to 60 days. The series of assessments conducted during this phase will determine eligibility for randomization into the study.

Inclusion criteria are discussed in Section 9.1 and detailed in Section 9.3.1. Before randomization the clinician will provide a judgment on the classification of a subject as either MCI/Prodromal or likely mild to moderate AD. (revised per Amendment 01) This judgment may be discussed and reviewed with the Sponsor or Sponsor's representative, as necessary.

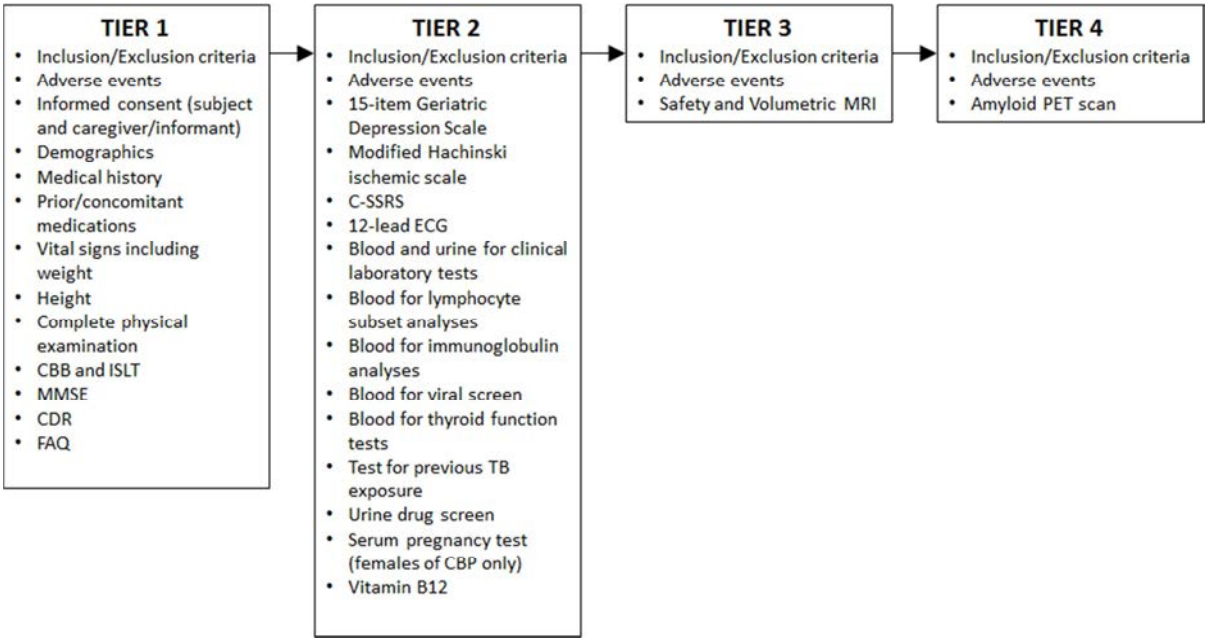
#### 9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and caregiver or informant, and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained from both the subject and the caregiver or informant. The caregiver or informant needs to be present at this visit.

Study site personnel will interview the subject and caregiver or informant to obtain demographic and clinical information as described in Table 6, and will review inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2 and perform any required assessments in order to complete these criteria. Prior medications and medications currently being taken by the subject will be reviewed (see Section 9.4.7). The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

Clinical assessments for eligibility will be conducted during the Screening Visit as described in Table 6 and Figure 2.

Every effort should be made to conduct these assessments in the morning, but if this is not possible, they should be conducted at the same time of day at all subsequent visits. The screening assessments/procedures have been organized into 4 distinct tiers (Table 6 and Figure 2). All assessments/procedures in each tier should be completed, and eligibility to continue screening in the study confirmed, before any assessments/procedures from the next tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures as long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. (revised per Amendment 01)




## Figure 2 Assessments to be Performed at Screening by Tier

CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), ISLT = International Shopping List Task (immediate and delayed recall), MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PET = positron emission tomography, TB = tuberculosis.

Cognitive assessments (Tier 1) are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). The order of assessments is: MMSE, CDR, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall) at Screening. The investigator will determine whether the caregiver or informant must attend in person or whether

telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session (Tier 3).

Amyloid PET imaging will be used to confirm all subjects have amyloid deposition in the brain (Tier 4).

#### 9.1.1.2 Baseline Period

All Screening Visit assessments must be completed (and eligibility to progress confirmed) before any Baseline Visit assessments are performed. The Baseline Visit assessments (per Table 6 and Section 9.5.1.2) are to be completed as soon as possible after completion of the final Screening Visit assessment (ie, PET scan) such that all Screening Visit and Baseline Visit assessments are completed within 50 days.

Inclusion and exclusion criteria will again be reviewed, vital signs including weight will be recorded, and a 12-lead ECG will be conducted in triplicate. A routine physical examination will be conducted and a dermatological assessment and neurological examination will be performed. A urine pregnancy test will be conducted for females of childbearing potential. Blood will be collected from all subjects for clinical chemistry and hematology, lymphocyte subset analyses, Ig analyses, and PD assessments. Blood samples will be collected and stored for determination of a subject's previous exposure to infective pathogens in the event of AEs that warrant further investigation occurring at a later point in the study. Psychometric assessments will be administered to the subject in the order stated in Table 6. The caregiver or informant needs to be present at this visit. The Columbia Suicide Severity Rating Scale (C-SSRS) will also be administered (Section 9.5.1.5.11).

CSF will be obtained at this visit for PK and PD assessments (see Section 9.5.1.5.3).

Blood will be collected from all subjects for pharmacogenomic (PGx) analyses of apolipoprotein E (*ApoE*) and the *NAT2* phenotype of subjects enrolled in the study (see Section 9.7.1.7.2).

### 9.1.2 Randomization Phase

Subjects who complete the Baseline Visit assessments, and are eligible based on the inclusion and exclusion criteria (see Section 9.3.1 and Section 9.3.2), will begin the Randomization Phase within 7 to 10 days following completion of the Baseline Visit assessments.

The Randomization Phase will consist of a Treatment Period of 78 weeks duration and a Follow-Up Period of 12 weeks after the last dose of study drug.

#### 9.1.2.1 Treatment Period

Subjects will be randomized at the beginning of the Treatment Period and will receive study drug or placebo, to be administered orally QD with food. Double-blinding to study drugs will be in effect throughout the Treatment Period. The dose for a subject will not be changed during the study. However, dose adjustment for Stage B may be considered and subjects

already randomized to a dose that needs to be adjusted will be switched to continue their treatment at the new adjusted dose.

Safety criteria for discontinuation of study drug are detailed in Section 9.3.3.

Subjects will attend the study site every week for the first 4 weeks after beginning study drug, then fortnightly until 12 weeks have elapsed since first dose. Visits will then be conducted at 16, 20, 26, 39, 52, 65, and 78 weeks after the first dose.

#### 9.1.2.2 Early Discontinuation

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug.

Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie. at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB and ISLT) will be conducted. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) after the Early Discontinuation Visit or within ± 8 days of either of the Follow-Up Visits (Visit 19 and Visit 20). Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

#### 9.1.2.3 Follow-up Period

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug (Visit 19) and a second 12 weeks after the last dose of study drug (Visit 20). If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the posttreatment Follow-Up period.

The end of the study will be defined as the date of the clinical database lock (ie, when all study data are collected and data validation is completed).

As required by some regulatory agencies, the following estimates are provided:

- The study will begin in Nov 2014 and is projected to end by Oct 2019 (end date will depend on actual recruitment rate).
- The maximum estimated period for each subject on study is anticipated to be approximately 2 years.

## 9.2 Discussion of Study Design, Including Choice of Control Groups

### 9.2.1 Overview

The 2 stage design of the study allows for the safety and tolerability of E2609 to be assessed in a limited number of subjects (n=60) before expanding recruitment into a larger population of subjects. (revised per Amendment 01)

The design of this study allows Proof of Concept to be established in subjects with MCI/Prodromal AD. The study also allows investigation of efficacy in subjects with mild to moderate AD to determine whether the effects of E2609 in this later stage population are comparable with those established in the MCI/Prodromal population within this same study (see Section 9.2.3 for discussion of the Bayesian design used in this study). (revised per Amendment 01)

The inclusion criteria for the MCI/Prodromal cohort will be consistent with the NIA-AA criteria for MCI due to AD (Albert, et al., 2011) and with the definition of Prodromal AD per Dubois et al., 2010 (see Section 9.2.2).

There is no active or positive control for this study as at this time, there is no cure for AD, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary efficacy tool for this Proof of Concept study is the composite scale ADCOMS (change from baseline in the derived ADCOMS at 18 months). The ADCOMS (Hendrix, et al., 2012) represents a novel composite approach integrating components of well established tools (ADAS-cog, MMSE, and CDR) to improve sensitivity to disease progression and treatment effects in subjects with AD (see Section 9.2.4).

Secondary efficacy endpoints include a biomarker of neuronal degeneration (shrinkage of neurons), which is the change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI; an amyloid biomarker, which is the change from baseline in CSF Aβ(1-x) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects; and a cognitive and functional assessment, which is the change from baseline in the derived ADCOMS at 18 months of treatment in mild to moderate AD subjects. (revised per Amendment 01) Exploratory endpoints including assessments of efficacy, safety and other biomarkers are also included.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

The rationale for the selection of doses used in the study is provided in Section 9.4.4.

### 9.2.2 Rationale for Study Population

By the time AD progresses to dementia, with loss of functional capabilities, the amyloid load in the brain is approaching a plateau and significant neurodegeneration has occurred (Jack, et al., 2010). Consequently, there is a growing view within the AD field that it may be necessary to initiate disease modifying treatments earlier, before the onset of clinical dementia (Aisen, et al., 2010). However, this hypothesis remains to be demonstrated with clinically effective therapies, and may not apply to all therapeutic classes, it is possible that this consideration explains the failure of the humanized monoclonal antibody bapineuzumab (which targeted brain amyloid) to demonstrate clinical efficacy in late-phase studies in mild-to-moderate AD dementia. (revised per Amendment 01)

With this consideration taken into account, the primary clinical population of focus in this study is subjects with MCI/Prodromal AD. The mechanism of action of a BACE1 inhibitor where amyloid production is reduced means E2609 is more likely to be efficacious (ie, slow disease progression) the earlier in disease progression treatment is started, where limited neurodegeneration has occurred and associated clinical deficits are at a minimum. However, since the effect of BACE1 inhibition along the AD continuum remains to be characterized, E2609 will also be evaluated for its profile in mild to moderate stages of AD, in the event data emerge supporting its use beyond MCI/Prodromal AD. Indeed, recent data support the notion of continued progression of amyloid pathology even in these later stages of the disease (Hu, et al., 2015), although at a slower pace, suggesting a positive effect of BACE inhibition and amyloid beta reduction cannot be ruled out even in the later stages of the disease trajectory. Hence, in this study, E2609 will be assessed in subjects with disease states ranging from MCI/Prodromal to mild and even moderate AD. (revised per Amendment 01)

As discussed, efficacy is more likely to be observed in subjects with MCI/Prodromal AD but there is the possibility that efficacy will also be evident following administration of an amyloid modifying agents such as E2609 in subjects with more advanced disease such as mild to moderate AD. (revised per Amendment 01) For example, a study of tarenflurbil, a selective Aβ(1-42)-lowering agent, on cognition and function in subjects with mild to moderate AD showed the subjects with mild AD had lower rates of decline than those in the placebo group in activities of daily living and global function; however, slowing of cognitive decline did not differ significantly (Wilcock, et al., 2008). Similarly, differential effects on cognitive measures have been observed with solanezumab, where some benefit from treatment was observed in subjects with mild AD, although studies with solanezumab were considered to have failed to improve cognition or functional ability significantly (Doody, et al., 2014). Therefore, it is relevant to compare the effect of the BACE1 inhibitor E2609 in 2 different subject populations that differ in terms of AD severity before the initiation of large Phase 3 clinical studies. (revised per Amendment 01)

### 9.2.3 Rationale for the Use of Bayesian Adaptive Design

This study uses a Bayesian adaptive design for the MCI/Prodromal cohort only in Stage B. This design optimizes subject allocation and evaluation of efficacy in a smaller number of subjects by maximizing the number of subjects exposed to doses of interest. Frequent

interim analyses will be performed to assess the probability of early success and futility and to aid in making early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis, such that subjects are more likely to receive a dose that is efficacious.

Subjects with mild to moderate AD will be assessed as a "nested" population that does not follow the Bayesian adaptive design. It was not considered appropriate to have a Bayesian design for both cohorts as this would have substantially increased the overall study sample size, delayed analyses of dose response, and would have added background "noise" for the comparison of subjects with MCI/Prodromal AD compared with those with mild to moderate AD. Data from each cohort will be analyzed independently for the purposes of decision making. A separate analysis of the 2 cohorts avoids the risk of data from subjects with mild to moderate AD confounding the results for the primary population (MCI/prodromal). (revised per Amendment 01)

### 9.2.4 Rationale for Clinical Endpoints

The ADCOMS (Hendrix, et al., 2012) was developed utilizing data from multiple studies to investigate responsiveness to progression and treatment effects rather than sensitivity to baseline deficits. The score was built empirically with no a priori assumptions, using a partial least squares regression model for placebo data from 4 MCI studies with a duration $\geq$12 months. A combination of cognitive and functional items was selected from a variety of well-established and validated scales that is most sensitive to change over time. The partial least squares regression coefficients from the model were used to form a weighted composite score comprising a total of 12 individual items taken from the ADAS-cog (4 items), the MMSE (2 items), and CDR (6 items), that assess both cognition and global function. Performance of the ADCOMS has been assessed against the original scales in several studies. The use of the ADCOMS allows for substantial sample size reductions in non-enriched and enriched MCI populations even over a 12-month period by increasing sensitivity. This derived score has shown adequate sensitivity in the MCI due to AD amyloid confirmed (CSF Aβ-positive) subgroup.

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007).

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The CDR is a clinical global rating scale requiring the interviewing of both the subject and an informant who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The CBB is a brief, computer-administered cognitive test battery that requires approximately 10 minutes for administration (Darby, et al., 2012; Fredrickson, et al., 2008; Maruff, et al., 2009). The CBB has been used to detect cognitive impairment in several neurodegenerative conditions including the measurement of cognitive function in healthy older adults and in adults with clinically diagnosed AD and prodromal AD (Darby, et al., 2009; Hammers, et al., 2012; Lim, et al., 2012a; Lim, et al., 2012b). The administration, scoring, and reporting of the CBB is automated and highly standardized, resulting in cognitive paradigms that have been well-validated in neuropsychological and cognitive studies (Fredrickson, et al., 2008; Maruff, et al., 2009). See Section 9.5.1.3.1 for further details.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al,. 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials on the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson et al., 2011, Lim, et al., 2012a, Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with E2609 treatment.

Volumetric magnetic resonance imaging is discussed in Section 9.2.5.4.

## 9.2.5 Rationale for Biomarkers

### 9.2.5.1 Overall Rationale

The biomarker strategy for this study includes the following aims:

- To establish an amyloid load in the brain at study entry (via the PET eligibility inclusion criterion)
- To evaluate safety (principally by magnetic resonance imaging [MRI])
- To confirm a PD effect in terms of both Aβ in CSF and brain amyloid assessed by amyloid PET and to establish that this PD effect is maintained long-term
- To evaluate disease modification through longitudinal assessments of vMRI, amyloid PET, and CSF biomarkers of neurodegeneration (tau and p-tau)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

#### 9.2.5.2 Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect of E2609 on Aβ(1-40) +Aβ(1-42) and other C-terminally truncated Aβ peptides such as Aβ(1-38) through inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using [$^{11}$C]PiB, suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases in CSF Aβ concentrations that are seen in AD are believed to be related to this decrease in brain Aβ availability.

Both total tau (t-tau) and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni and Bhaskar, 2012). CSF tau measurements have been correlated with cerebral atrophy, while their ratios with Aβ42 have provided useful predictors of cognitive decline and progression to dementia due to AD. Rebalancing dysregulated amyloid production early in the process may positively affect the neurodegenerative process and thus affect these markers and benefit the disease trajectory. Therefore, monitoring these markers in conjunction with amyloid imaging may provide further supportive evidence of efficacy.

Baseline levels of Aβ(1-42), tau, and p-tau will also help elucidate the extent of AD pathology at entry to the study and can be combined with baseline levels of *ApoE4* genotyping in addition to the baseline imaging variables to help explain differences in treatment response.

The study will be stratified at randomization for *ApoE4* gene status in order to account for any *ApoE* status by treatment interaction or *ApoE* status by amyloid-related imaging abnormalities risk interaction.

#### 9.2.5.3 Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) to confirm the presence of AD pathology in the brain of subjects with MCI/Prodromal AD or mild to moderate AD at entry to the study; and 2) to evaluate the effects of E2609 on amyloid levels in the brain, both by whole brain analysis (the average of 5 to 6 cortical regions) and brain region analysis. (revised per Amendment 01)

Longitudinal amyloid PET imaging will be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug) as an exploratory measure of the potential disease-modifying effects of E2609. Longitudinal amyloid PET imaging will only be conducted until 18-month PET scans of acceptable quality have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used.

#### 9.2.5.4 vMRI

Volumetric imaging will be used to evaluate the effects of E2609 on rates of atrophy across the different dose groups and to provide support that effective treatment is associated with modification of disease course (secondary endpoint for the MCI/Prodromal population and exploratory endpoint for the mild to moderate AD population). (revised per Amendment 01) A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. Clinically efficacious doses are predicted to be associated with a slowing in the rate of hippocampal atrophy compared with rates observed in the placebo and non-efficacious dose groups. Treatment effects on left and right hippocampal, whole brain, and total ventricular volumes are exploratory endpoints.

Annualized rates of change of 2% to 3% have been reported for the AD brain compared with 1% in MCI and <1% in age-matched controls (Hua, et al., 2010, Leung, et al., 2010). However, subjects with MCI due to AD-dementia (CSF Aβ <192 pg/ml or positive amyloid imaging) show rates of atrophy comparable to those observed in subjects with AD-dementia (Hua, et al., 2009; Hua, et al., 2010; Leung, et al., 2010; Morra, et al., 2009), supporting the notion that such subjects are on similar trajectories as those with mild AD-dementia. Lower levels of CSF Aβ42, amyloid positivity on PET imaging, and higher levels of CSF tau in addition to the presence of the *ApoE4* allele have all been associated with greater rates of brain atrophy (Fjell, et al., 2010a; Fjell, et al., 2010b) and will be entered as covariates in various analyses. Hippocampal atrophy has also been shown to predict clinical progression independently of amyloid levels in the brain (Jack, et al., 2010), and this measure will be entered as a covariate in the analysis of the clinical endpoints along with the aforementioned variables.

Brain volume (total ventricular volume, whole brain, temporal lobe) generally shows a modest correlation with performance on a number of cognitive scales (Hua, et al., 2009; Hua, et al., 2010; Freeborough, et al., 1997; Leung, et al., 2010). Using volumetric analysis performed at 6-month intervals, these relationships and the effects of E2609 treatment will be explored further. Recent advances in analysis software have made structural imaging more sensitive to detect small changes and able to reliably measure rates of atrophy at these intervals, particularly in the posterior parietal and the lateral temporal regions during the early stages of disease (Hua, et al., 2009; Hua, et al., 2010). Given these observations, a demonstration of significant slowing or stabilization in the rate of atrophy in response to treatment, compared with placebo, will offer further support for disease modification.

### 9.2.6 Clinical Risks and Mitigation Strategy

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, and to mitigate clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. These safety aspects include the following:

- Two-stage study design: there will be a pause in recruitment after 60 subjects have been randomized to study drug (Stage A). Only after the safety of E2609 in these first 60 subjects (consisting of up to 12 weeks data for the later subjects and longer dosing periods for the earlier subjects) has been reviewed by the DSMB and considered acceptable, will randomization of further subjects into the study commence (Stage B). (revised per Amendment 01)
- Immunology-related and infection-related exclusion criteria
- Review of unblinded safety data by an independent DSMB at regular intervals
- Safety criteria for discontinuation of study drug based on CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cell) and other lymphocytes (absolute counts and percentage change from baseline), skin rash, reoccurrence of herpes virus infections including any oral herpes, genital herpes or shingles, other infections, MRI changes, ECGs, and pregnancy.

In addition to the features above, other safety aspects of this study designed to mitigate clinical risk include the following:

- Blinded safety data will be monitored by Eisai at regular intervals during the course of the study
- Routine safety assessments will include the monitoring and recording of all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events. To assess potential immunomodulatory effects, peripheral blood mononuclear cells (PBMCs) will be collected at baseline, during treatment, and posttreatment.

As per the communication from the Food and Drug Administration (FDA) in Aug 2013, there are concerns that hypopigmentation of the skin and mucous membranes may occur with BACE1 inhibitory drugs. Although no such effects have been seen with E2609 to date, assessments by a reviewing dermatologist will be performed at regular intervals during the study. These assessments will be made centrally, using standardized photography and will specifically include evaluation of any areas of depigmentation or any rash. Dermatological assessments will be supplemented with a specific question to subjects regarding skin changes at each visit. Any such changes could be referred to the central reviewing dermatologist, and to a local dermatologist if needed, for further evaluation. See Section 9.5.1.5.8 for further details.

- Baseline and on-study blood, DNA, and CSF samples will be taken and stored for all subjects. These samples may be tested in the event that a subject develops AEs that warrant further investigation (eg, if a subject develops a treatment-emergent infection) (see Section 9.5.1.2.2).

- Central reading of safety brain MRI assessments (including any MRI evidence of demyelination) will be performed at Screening, at approximately 6-month intervals during the Treatment Period, and at the final Follow-Up Visit.
- Full neurological examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations. Details of the neurological examination are given in Section 9.5.1.5.9.
- Cognitive decline will be assessed as a safety assessment (ADAS-cog$_{14}$, MMSE, and CBB). Of particular importance will be the assessment of reaction time testing using the detection and identification tasks on the CBB.
- An assessment of suicidality using the C-SSRS will be performed at Screening, Baseline, and at regular intervals during the Treatment and Follow-Up Period (see Section 9.5.1.5.11).
- All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will have at least 2 off-treatment Follow-Up visits (4 and 12 weeks after the last dose of study drug). More frequent safety assessments can be made as unscheduled assessments/visits during the off-treatment Follow-Up period, if clinically indicated.
- An ophthalmic examination will be conducted at Baseline and if the subject experiences visual disturbances during the course of the study (see Section 9.5.1.2.1).

## 9.3 Selection of Study Population

Stage A will randomize 60 eligible MCI/Prodromal or mild to moderate AD subjects at approximately 30 sitesin the United States. There will be no restriction to the number of subjects from either population. Stage B will randomize subjects at approximately 125 sites globally. Recruitment will continue in Stage B until a maximum of approximately 500 MCI/Prodromal subjects and up to a maximum of approximately 200 mild to moderate AD subjects have been randomized (including subjects randomized during Stage A). The final total number of MCI/prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. The number of mild to moderate AD subjects randomized in Stage B will depend upon the number of mild to moderate AD subjects randomized during Stage A. (revised per Amendment 01)

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

### 9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD (Albert, et al., 2011) or AD dementia (McKhann, et al., 2011) and is "staged" or classified as either MCI or mild to moderate dementia and also complies with the following: (revised per Amendment 01)

**Required at both Screening and Baseline:**

a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation
b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT
c. FAQ ≤24 (revised per Amendment 01)
d. MMSE ≥16 (revised per Amendment 01)

2. Amyloid positive PET image based on centralized PET scan reading
3. Male or female, age 50 to 85 years, inclusive at time of consent
4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.
5. If receiving acetylcholinesterase inhibitor (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the Baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.
6. Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization

### 9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or MRI
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of

simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.

5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (however, lesions diagnosed as arachnoid cysts and < 1cm in diameter at their greatest diameter need not be exclusionary) or brain tumors (eg, meningioma). (revised per Amendment 01)
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could confound the MCI/Prodromal or mild to moderate AD diagnosis or could interfere with study assessments or procedures (revised per Amendment 01)
7. A score of ≥8 on the 15-item Geriatric Depression Scale (GDS) at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the LLN for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
12. Any contraindications to lumbar puncture (LP) for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity)
13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of Ig deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection

19. Any live vaccine in the 3 months before randomization.
20. Any active infection within the last 4 weeks prior to randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests conducted at Visit 2 (eg, MMSE, CDR) must be repeated.
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below LLN and confirmed by a repeat test conducted 1 week after the initial test
23. Ig (IgG, IgA, or IgM) levels below the LLN at Screening or Baseline, unless both the Investigator and the Medical Monitor agree that the finding is not clinically significant. The assessment of clinical significance will include, but not be limited to, evidence of clinical immunodeficiency. The discussion with the Medical Monitor should include a detailed review of medical history of infections, clinical and laboratory findings. (revised per Amendment 01)
24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate ECGs. A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute (bpm) at Screening or Baseline
29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled

32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.
33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the C-SSRS suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized

partner with confirmed azoospermia) throughout the entire study treatment period or for-28 days after study drug discontinuation.

- Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.
- Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.

  (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

44. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or not practicing highly effective contraception throughout the study period or for 28 days after study drug discontinuation). No sperm donation is allowed during the study period and for 28 days after study drug discontinuation.

### 9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may discontinue study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to stop study drug or withdraw from the study at any time for any reason.

Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug (see Section 9.1.2.3). Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie. at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB and ISLT) will be conducted. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) after the Early Discontinuation Visit or within ± 8 days of either of the Follow-Up Visits (Visit 19 and Visit 20). Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the Subject Disposition eCRF page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study drug and withdraws from the study at the same time, the ED Visit will be followed (see Section 9.5.5).

Safety-related criteria for discontinuation of study drug include the following:

a. A study drug discontinuation threshold will be set based on absolute counts of CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells). The discontinuation threshold will be set at below the level of the LLN, at a level that represents a greater risk of opportunistic infection in the treated population. For CD4 (T helper cells) the discontinuation threshold is 250 cells/μL. For CD8 (cytotoxic T cells) and CD19 (B cells) the discontinuation thresholds are 150 cells/μL and 50 cells/μL, respectively. Any subject who has CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below the discontinuation threshold as confirmed by a repeat test conducted within 1 week of the initial test will be discontinued from study drug.
b. Subjects with CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between the LLN and the discontinuation threshold will have lymphocyte subset counts performed on a weekly basis. Subjects with a >33% reduction from baseline in CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts will also have lymphocyte subset counts performed on a weekly basis. For these subjects, the decision as to whether the subject remains on study drug or is to be discontinued from study drug will be based upon clinical judgment and will take into account any clinical presentation in addition to the lymphocyte subset counts. These subjects may continue with treatment if there is no clinical evidence of infection. They will be discontinued from study drug if they have infections of a moderate to severe intensity (eg, subjects whose infections are not localized, or are systemically unwell, or who require systemic antiinfective drug treatment).

**Table 1 Study Drug Actions for Lymphocyte Subset Absolute Counts**

| Lymphocyte subset absolute counts | Action | Decision to continue or discontinue |
|---|---|---|
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold | Retest within 1 week | If retest performed within 1 week confirms lymphocyte subset counts below the discontinuation threshold, discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between LLN and discontinuation threshold or >33% reduction from baseline in CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts | Lymphocyte subset counts to be performed weekly until counts return to ≥ LLN or no more than 33% reduction from baseline | Decision will be based upon lymphocyte subset counts and clinical judgment |

LLN = lower limit of normal.

c. Subjects with clinical evidence of infection will have their CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts measured. Blood and other biological samples will also be collected for investigations of infective pathogens (eg, serological tests, quantitative polymerase chain reaction, microscopy, and culture) where appropriate. In subjects with infection, if any of their absolute cell counts meets the discontinuation thresholds, study drug will be discontinued. All subjects with severe infections will be discontinued from study drug. All subjects with herpes zoster (shingles) or ocular herpes infections will be discontinued from study drug, regardless of severity of presentation. Subjects with mild or moderate infection may continue

treatment with study drug unless otherwise clinically indicated or otherwise specified below. Specifically, when any of the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are between the LLN and the discontinuation thresholds or have shown >33% reduction from baseline, subjects with infections of moderate intensity will be discontinued from study drug (eg, subjects whose infections are not localized, or subjects who are systemically unwell, or who require systemic antiinfective drug treatment). All subjects with infection who are discontinued from study drug will be followed for a period of 12 weeks or until the infection resolves/ stabilizes or until the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts have returned to >LLN (whichever comes latest).

**Table 2 Study Drug Actions for Lymphocyte Subset Absolute Counts and Infection**

| Criterion | Severity of Infection | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold | Discontinue study drug | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between LLN and discontinuation threshold or >33% reduction from baseline in CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts | May continue treatment with study drug unless clinically indicated | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts always >LLN and no reduction from baseline >33% | May continue treatment with study drug unless clinically indicated | May continue treatment with study drug unless clinically indicated (See (e) for exception) | Discontinue study drug |

LLN = lower limit of normal.

d. A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (see (e) for exception), will be discontinued from study drug and a dermatological consult will be requested regardless of whether the rash is considered drug-related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatological consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

e. Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

f. Development of any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. If discontinued from study drug, subjects will undergo an ED Visit within 7 days after discontinuation and will attend the Follow-Up Visits 4 and 12 weeks after the last dose of study drug. They will also undertake an Unscheduled Visit (with MRI) at approximately 4 weeks after the visit at which such MRI features were first identified. An MRI will also

be performed at approximately the time of the second Follow-Up Visit (Visit 20). Additional visits for safety may be arranged if clinically indicated in the opinion of the investigator, including after 12 weeks after the last dose of study drug. At any time during the treatment period, subjects who have asymptomatic, treatment-emergent microhemorrhages as detected by MRI, but none of the features which merit discontinuation of treatment (ie, vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic treatment-emergent microhemorrhage) may continue with treatment. These subjects will have safety assessments (including MRI) at approximately 4 weeks after the visit at which such MRI features were found. They will also continue with the scheduled MRI scans. Additional unscheduled MRI scans may be arranged on an individual subject basis in discussion with the study medical monitor.

g. A postdose ECG with an average QTcF interval >500 msec from triplicate ECGs
h. A postdose ECG with a QTcF interval increase from baseline >60 msec and a QTcF interval >450 msec as demonstrated from triplicate ECGs
i. Any seizure (motor or non-motor)
j. Pregnancy

## 9.4 Treatments

### 9.4.1 Treatments Administered

For this study the test drug is E2609 and the control drug is placebo. All study drugs are to be administered orally, QD, with food.

Treatments to be administered in Stage A and Stage B are shown below and in Figure 1.The 2 highest E2609 doses (15 mg and 50 mg) taken into Stage B, after the PK/PD and safety review from Stage A, will be used for the mild to moderate AD population in Stage B. (revised per Amendment 01)

- Stage A: 3 doses (5 mg, 15 mg, and 50 mg) of E2609 or placebo
- Stage B, MCI/Prodromal Cohort: 3 doses (5 mg, 15 mg, and 50 mg) of E2609 or placebo
- Stage B, Mild to Moderate AD Cohort: 2 doses (15 mg and 50 mg) of E2609 or placebo. (revised per Amendment 01)

Study treatment will begin on Day 1 (at the study site) following Randomization and will continue for approximately 78 weeks. Please refer to Table 7 and Section 9.5.1.4.1 for specific information on drug administration on days when PK sampling is to be performed.

Study drug doses will remain the same for each individual subject unless the interim PK/PD analysis determines that an entire dose level requires adjustment (Section 9.4.4). See Section 9.3.3 for safety-related discontinuation criteria of study drug. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

### 9.4.2 Identity of Investigational Product

E2609 tablets of 5-mg, 10-mg and 25-mg dose strengths will be supplied. Placebo tablets of identical appearance will also be available. Each subject will receive 2 tablets, which combined will make up the required doses of E2609 5 mg, E2609 15 mg, E2609 50 mg, or placebo. The tablets will be supplied by the Sponsor in labeled blister packs. The product release certificates for E2609 and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either E2609 or placebo, or both (see Section 9.4.2.3 for labeling details).

#### 9.4.2.1 Chemical Name and Formula of E2609

- Test drug code: E2609
- Generic name: not applicable
- Chemical name: International Union of Pure and Applied Chemistry
- *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

#### 9.4.2.2 Comparator Drug

Not applicable.

#### 9.4.2.3 Labeling for Study Drug

E2609 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier (ID)
- Lot number/batch number
- Storage conditions, expiration date if necessary

#### 9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

### 9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used for Stage A (all subjects), for Stage B MCI/Prodromal subjects and Stage B for mild to moderate AD subjects are described in Section 9.4.1. (revised per Amendment 01)

Randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized blister card identification numbers. At enrollment, the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 3), the IxRS will assign each subject a unique randomization number.

### 9.4.4 Selection of Doses in the Study

It is not known how the level of CSF or brain Aβ reduction is related to clinical efficacy. Therefore, in this study, doses will be selected such that at steady state, they will result in 25%, 50%, and 75% reduction in CSF Aβ levels from baseline to cover a broad range of PD effects.

In Study 007, the relative bioavailability of a tablet formulation of E2609 in the fed and the fasted states compared with the capsule formulation in the fasted state (used in Studies 001 and 002) was investigated. It was found that when the tablet form of E2609 (50 mg) was administered with food, the exposure (ie, AUC) of the parent drug E2609 was higher, with lower maximum observed concentrations and reduced exposure to the metabolites, compared with either formulation in the fasted state.

Based on the PK/PD modeling using data from healthy volunteer Studies 001, 002, and 007, doses of 5 mg, 15 mg, and 50 mg QD administered as the tablet formulation with food in this study should achieve CSF Aβ reduction from baseline of approximately 25%, 50%, and 75% at steady state, respectively (Table 3).

**Table 3 Predicted Steady State Plasma PK Parameters and CSF Amyloid β Reduction From Baseline**

| E2609 Tablet Daily Dose (mg) With Food | E2609 Plasma $C_{max,ss}$ (ng/ml) | E2609 Plasma $C_{ss,av}$ (ng/ml) | E2609 Plasma $AUC_{(0-24h)ss}$ (ng.h/ml) | % Reduction CSF BACE1 Activity | % Reduction CSF Aβ(1-x) |
|---|---|---|---|---|---|
| 5 | 6.2 | 3.3 | 80.3 | 16.2 | 33 |
| 15 | 18.6 | 10 | 240.9 | 36.6 | 56 |
| 50 | 62.1 | 33.5 | 803.0 | 65.7 | 79 |

Aβ(1-x) = amyloid beta monomer from amino acid 1 to x, $AUC_{(0-24h)ss}$ = area under the concentration x time curve at steady state from time zero to 24 hours, BACE1 = Beta-amyloid converting enzyme, CSF = cerebrospinal fluid, $C_{ss,av}$ = average steady-state concentration, $C_{max,ss}$ = maximum plasma concentration at steady state, PK = pharmacokinetics.

The PK/PD modeling described above, which was conducted using data obtained from healthy volunteers, has also been supported by modeling of data from subjects with an underlying AD pathology (Study 101). Furthermore, external data with another BACE1 inhibitor (MK-8931) showed a similar PD effect in AD patients as in healthy volunteers (Forman, et al., 2013). Therefore we are confident that the modeling of E2609 effects in healthy subjects will be applicable for both MCI/Prodromal and mild to moderate AD dementia patients. (revised per Amendment 01)

The exposure of the highest dose in this study (50 mg QD tablet administered with food) is less than that of the 100 mg QD dose (capsule administered fasted) in Study 002.

The 100 mg QD dose administered for 14 days in Study 002 was well tolerated with no clinically significant changes in laboratory parameters, vital signs, or ECG parameters. On Day 15, for the 100 mg QD cohort in Study 002, there was a reduction of CD4 lymphocyte counts compared with placebo (CD4 lymphocyte counts on E2609 decreased by 3.1% from baseline, whereas the placebo control showed an increase of 8.7%), but this decrease was less than that observed at doses of 200 mg (22.9% decrease) or 400 mg (17.3% decrease). No subjects had infections or drug rash while receiving E2609 100 mg QD or at lower doses in Study 002, whereas at 200 mg and 400 mg QD, 4 subjects had symptomatic orolabial HSV1 relapses and 2 subjects at the highest dose had drug rash. The highest dose for Study 202 of 50 mg QD (tablet administered with food) is therefore expected to have a similar or better safety profile compared with the 100 mg QD capsule (administered fasted) in Study 002. Specific exclusion criteria, blinded and unblinded safety monitoring procedures, and safety criteria for discontinuation from study drug are included in this study in order to mitigate any immunology-related risk with E2609, particularly in light of the progression from 14 days of dosing (Study 002) to 18 months of dosing in this study.

In Stage A, all subjects will be randomized to receive either placebo or E2609 at 5 mg, 15 mg, or 50 mg QD. In Stage B, subjects in the MCI/Prodromal cohort will continue to be randomized to receive either placebo or E2609 at 5 mg, 15 mg, or 50 mg QD. In Stage B, subjects in the Mild to Moderate AD cohort will be randomized to receive either placebo or E2609 at 15 mg or 50 mg QD, but not the 5-mg QD dose. The rationale for not including an E2609 5-mg QD dose in the dose regimens for Stage B subjects with mild to moderate AD is

that more advanced disease may require greater reduction in CSF Aβ levels for comparable effects. (revised per Amendment 01)

After 60 subjects in Stage A have completed 4 weeks of treatment, an interim analysis of the E2609 PK and PD profiles will be used to confirm the E2609 doses to be used for Stage B, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels. (revised per Amendment 01) If the 95% confidence interval of the mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment with a dose of E2609 does not include its intended target value (ie, 25%, 50%, and 75% reductions from baseline, respectively for E2609 at 5 mg, 15 mg, and 50 mg), PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data from Stage A and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline after 4 weeks of dosing. From this model, the new target plasma steady state concentrations of E2609 required to achieve the target levels of CSF Aβ(1-x) reduction will be estimated again. Dose adjustment for Stage B may be considered if it is possible to get closer to the new target plasma steady state concentrations of E2609 required to achieve the intended target levels of CSF Aβ(1-x) reduction than is possible with the initially planned doses, given the limitation that E2609 dose adjustments will have to be in 5-mg increments or decrements. Subjects already randomized to a dose that needs to be adjusted will be switched to the new adjusted dose and complete their treatment at this new dose.

If dose adjustment is required for Stage B, a protocol amendment reflecting the new doses will be submitted.

### 9.4.5 Selection and Timing of Dose for Each Subject

E2609 is administered orally, QD, with food. Study treatment will begin on Day 1 following randomization and will continue for approximately 78 weeks.

### 9.4.6 Blinding

E2609 and placebo will be administered as tablets of identical appearance.

During the Randomization Phase and Follow-Up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and Eisai staff will be blinded to the treatment codes (double-blind).

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (ie, those who are trained and certified to perform the various cognitive assessments that are undertaken in this study). Furthermore, at the site, the notes and reports relating to safety assessments must be kept separate from the notes and reports relating to efficacy, particularly for the CDR. (revised per Amendment 01)

Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

The PK/PD interim analysis to confirm the E2609 doses to be used for Stage B will be conducted by an independent group. Any changes to dose will be reflected in an amendment to the protocol and the Statistical Analysis Plan will detail how data will be handled in the primary analysis.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

At the conclusion of the study, all unused drug supplies are to be returned to the Eisai approved contract packaging vendor.

### 9.4.7 Prior and Concomitant Therapy

Medication (including over-the-counter medications) or therapy administered to the subject before the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2. Prohibited medications are presented in Listing 1, Listing 2, Listing 3, Listing 4, Listing 5, and Listing 6. Medications that are permitted with restrictions are listed in Listing 7, Listing 8, and Listing 9.

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit:

- Anticoagulants (eg, warfarin, digabatrin) are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization
- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization

- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization

Subjects taking AChEIs or memantine must meet the following criteria in order to be included in the primary analyses:

- On a stable dose for 12 weeks before the Baseline cognitive assessments at Visit 2
- Remain on a stable dose while on study

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for the primary analyses.

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety, and are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks.

### 9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period. CRAs will review treatment compliance during site visits and at the completion of the study.

### 9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator

- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the principal investigator including a copy of the principal investigator's current medical license (required for United States sites) or medical registration number on the curriculum vitae
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site

but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

## 9.5 Study Assessments

### 9.5.1 Assessments

#### 9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

#### 9.5.1.2 Baseline Assessments

Assessments to be made at Screening and Baseline and throughout the study are described in Section 9.5.1.3, Section 9.5.1.4, and Section 9.5.1.5.

##### 9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, current medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment due to AD. Subjects will be asked about history of TB, infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV Types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include onset, duration, relapse frequency, severity, and treatments. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The 15-item GDS and modified Hachinski ischemic scale will also be assessed at Screening as part of the exclusion criteria.

Physical examinations (complete or routine) will be performed as designated in Table 6. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat,

neck, chest (including heart and lungs), abdomen, limbs, and skin, and a neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### 9.5.1.2.2 VIRAL TESTING

As specified in Table 6, blood will be collected for screening for Hepatitis B and Hepatitis C for determining eligibility, and at Baseline for viral characterization.

#### 9.5.1.2.3 B12 TESTING

Blood will also be collected for vitamin B12 levels as specified in Table 6.

#### 9.5.1.2.4 TB EXPOSURE TESTING

Blood will also be collected for testing for previous TB exposure, as specified in Table 6.

#### 9.5.1.2.5 URINE DRUG TESTING

Urine will be collected for drug screening as specified in Table 6.

### 9.5.1.3 Efficacy Assessments

#### 9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

The timing of psychometric assessments is shown in Table 6 and Table 7. These assessments should be administered in the morning (or, if not possible, consistently at the same time of day) and should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The order of assessments is: MMSE, CDR, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall) at Screening; and MMSE, CDR, ADAS-cog$_{14}$, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall) at the Baseline Visit.

At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

**The Derived Alzheimer's Disease Composite Score:** The primary efficacy endpoint is the change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects.

The ADCOMS is derived from the ADAS-cog (4 items), the MMSE (2 items), and the CDR (all 6 items), described below. The ADCOMS is more sensitive to clinical progression

compared with currently existing clinical batteries and requires smaller sample sizes for clinical studies in MCI/Prodromal AD or mild to moderate AD. (revised per Amendment 01) It also shows sensitivity to treatment effects with AChEIs. The ADCOMS assesses both cognitive and functional domains and can be offered as a single primary clinical endpoint. The ADCOMS has a range from 0 to 1.97.

**CogState Brief Battery:** The CBB is a computer-based battery comprising 4 cognitive tests:

1. Detection – a simple reaction time test where the subject presses a key when the card is turned face up from a pack of cards ("Has the card turned over"). Speed of response is the measure.
2. Identification – a simple choice reaction time test where the subject presses 1 of 2 keys when the card just turned face up is either a red card or a black card ("Is the card red"). Speed of response is the measure.
3. One Card Back – a simple working memory test where the subject presses 1 of 2 keys when the card turned face up is either the card seen in the immediately previous trial or not ("Is the previous card the same"). Accuracy of response is the measure.
4. One Card Learning – a visual learning and memory test where the subject presses 1 of 2 keys depending on whether the card just turned face up has been seen before or not in the task ("Have you seen this card before in this task"). Accuracy of response is the measure.

**ISLT:** The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 15 minutes, in which time the CBB is performed, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

**Mini Mental State Examination:** A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

**Clinical Dementia Rating:** The CDR assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

**Alzheimer's Disease Assessment Scale - cognitive subscale:** Discussed in Section 9.2.4.

**Functional Assessment Questionnaire:** Either a caregiver or informant or the subject provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

#### 9.5.1.3.2 VOLUMETRIC MRI

Volumetric MRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the Alzheimer's Disease Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

Volumetric MRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. Volumetric MRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. Volumetric MRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 6 and Table 7, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

CSF samples will be collected by LP (gravity drip method) at the timepoints specified in Table 6 and Table 7. The CSF sample taken at the Baseline Visit will only be performed after confirmation of an amyloid positive PET scan. See Section 9.5.1.4.2 for further details.

### 9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

#### 9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood and CSF samples will be collected for the determination of the concentrations of E2609. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with E2609.

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 6 and Table 7. Two PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visits 5, 11, 14, and 16, and 4 to 8 hours postdose at Visit 7 and Visit 18 (or at the ED Visit). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug with food at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or

at the ED Visit) the PK blood sample should be collected shortly before or shortly after completing the LP. (revised per Amendment 01) Although the PK sampling procedures at the ED visit should follow those of Visit 18, in the event that study drug has already been discontinued prior to the ED visit, then no dosing will be conducted. However, a PK sample at trough (before LP) will be collected, followed by LP at approximately the same time as previous visits. A second PK blood sample will be collected as close as possible in time to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

#### 9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

**Biomarkers**

Subjects will be encouraged to stay at the site after completion of LP for medical observation. At Baseline, a CSF sample will be collected by LP (gravity drip method) after fasting (preferred), or at least 2 hours after the most recent meal. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. At visits where cognitive tests are also performed, if the tests are to be performed on the same day, the LP must be performed after the cognitive tests have been completed and the subjects should rest and drink some fluid to hydrate before the LP. (revised per Amendment 01) The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. The CSF sample will be used for PD assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), t-tau, p-tau, and BACE. The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses (eg, miRNA). Aβ(1-x) in both CSF and plasma will be measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and post-screening analysis of CSF Aβ(1-42), t-tau, and p tau will be performed using ELISAs. BACE1 levels will be measured using internally developed fluorescence resonance energy transfer and ELISA based assay(s). Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

The blood sample collected for PD analyses at Baseline should be collected on the same day shortly before or shortly after completing the LP at Baseline. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

At the Baseline Visit, CSF and blood samples will be collected and stored for determination of prior exposure to any suspected infective agents in the event that the subject develops treatment-emergent AEs that warrant further investigation (eg, treatment-emergent infection). Testing may include, but not be limited to, serological tests, viral titer by quantitative polymerase chain reaction, or human leukocyte antigen genotyping.

Blood samples will be collected for PD assessments as specified in Table 6 and Table 7. See Section 9.5.1.4.2 for further details.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

**Pharmacogenomics**

A blood sample will be obtained at Baseline and will be used to determine the *ApoE* genotype (homozygous or heterozygous E4 versus non-E4) and the *NAT2* phenotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response, safety, or PK of E2609. Details of which genotype / phenotype data will be applied to the analyses of efficacy, safety or PK will be discussed in the Statistical Analysis Plan.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

**Amyloid PET**

An amyloid PET scan will be performed at Screening to confirm deposition of amyloid in the brain. Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted until acceptable 18-month PET scans have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used (Table 6). PET scanning will be performed with a locally approved Aβ imaging agent, eg, Amyvid. Descriptions and detailed instructions for all imaging can be found in the imaging manual.

Amyloid PET imaging is an exploratory measure of the potential disease-modifying effects of E2609.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, lymphocyte subsets, Igs, and urine values; periodic measurement of vital signs and ECGs; performance of physical and neurological

examinations; centralized dermatological assessments; the C-SSRS; and safety MRIs as detailed in Table 6 and Table 7 will also be conducted. Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and posttreatment for exploratory immunomodulatory and immune-based analyses.

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments, particularly for the CDR (see Section 9.4.6). (revised per Amendment 01)

#### 9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E2609.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: It is not necessary to report every sign or symptom as a separate AE if the overall disease [diagnosis] is being reported as an AE.)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, discontinuation of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 20, as shown in Table 7). For subjects who discontinue early from study drug but undertake further efficacy assessments, AEs will only be collected for 3 months after the last dose of study drug, ie, through to the second follow-up visit (Visit 20). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF. SAEs will be collected for 3 months after the last dose of study drug, ie, through to the second follow-up visit (Visit 20). For subjects who discontinue early from study drug but continue with further efficacy assessments, SAEs will be solicited only for 3 months after the last dose of study drug, i.e. up to the 2nd follow up visit (Visit 20). However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the ADCOMS, ADAS-cog$_{14}$, MMSE, and CBB (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 4.

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis
- Dissociative state

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.11 for a description of the C-SSRS).

The following adverse events will require the collection of information sufficient to provide a detailed description of the event, treatment and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection; any moderate to severe drug rash or any rash lasting more than

72 hours (regardless of severity); amyloid-related imaging abnormalities (vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a "yes" answer to Type 4 or 5 suicidal ideation, or a "yes" response to any suicidal behavior on the C-SSRS.

All AEs must be followed through the second follow-up visit (Visit 20), or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

**Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.**

### Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

| | |
|---|---|
| Mild | Discomfort noticed, but no disruption of normal daily activity |
| Moderate | Discomfort sufficient to reduce or affect normal daily activity |
| Severe | Incapacitating, with inability to work or to perform normal daily activity |

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

### Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

#### *Classification of Causality*

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

#### 9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reportable using the criteria of important medical event if the event does not meet other serious criteria: new onset seizures, ocular herpes.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the eCRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)

- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

#### 9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 4. Subjects should be in a seated or supine position during blood collection. Table 6 and Table 7 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

See Section 9.3.3 for safety criteria for discontinuation from study drug related to absolute counts of CD4, CD8, and B lymphocytes, and for lymphocyte subset counts.

**Table 4 Clinical Laboratory Tests**

| Category | Parameters |
|---|---|
| **Hematology** | Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), and (Screening and Beseline only), PT, PTT, and INR |
| **Chemistry** | |
| **Electrolytes** | Bicarbonate, calcium, chloride, phosphate, potassium, sodium |
| **Liver function tests** | Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin |
| **Renal function tests** | Blood urea/blood urea nitrogen, creatinine |
| **Other** | Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid |
| **Urinalysis** | Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells |
| **Other** | Lymphocyte subset analyses (see Table 5). Regulatory T cells will be measured using CD4, CD25, and CD127 cell surface markers and FoxP3 intracellular marker.<br>PBMCs<br>Ig analyses (IgG, IgA, and IgM).<br>Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]).<br>Viral characterization (including HSV1, HSV2 and CMV, etc)<br>Serum pregnancy test (females of child bearing potential only)<br>Tuberculosis Interferon Gamma Release Assays<br>Tests for thyroid function (thyroid stimulating hormone, free triidothyronine and free thyroxine) and vitamin B12<br>Blood sample for storage for subsequent testing of immune status<br>Cerebrospinal fluid sampling |

CMV = cytomegalovirus, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV = herpes simplex virus, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononeuclear cell, PT = prothrombin time, PTT = partial thromboplastin time.

The 8 different surface markers (CD3, CD4, CD8, CD45, CD19, CD16, CD56, and CD14) and total lymphocyte counts will be measured in order to provide the lymphocyte subset data as shown in Table 5. In addition, Regulatory T cells will be measured using CD4, CD25, and CD127 cell surface markers and FoxP3 intracellular marker.

**Table 5 Lymphocyte Subtyping**

| Cell Type | Cell Surface Markers |
|---|---|
| T lymphocytes | CD3 |
| T helper cells | CD3+, CD4 |
| Cytotoxic T cells | CD3+, CD8 |
| Mature B cells | CD3-, CD19 |
| Natural killer cells | CD3-, CD16, CD56 |
| Macrophages | CD14 |

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the case report form [CRF] Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

#### 9.5.1.5.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [bpm], respiratory rate [per minute], body temperature [in centigrade], and weight [kg]) will be obtained at the visits designated in Table 6 and Table 7 by a validated method. Measurements of sitting BP and heart rate will be obtained. All BP measurements should be performed on the same arm, preferably by the same person.

#### 9.5.1.5.5 Physical Examinations

A complete physical examination will be performed at Screening as described in Section 9.5.1.2.1. At Baseline and during the Randomization Phase, routine physical examinations will take place as shown in Table 7. These examinations will include the cardiovascular system, respiratory system, and neurological system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.6 Electrocardiograms

Electrocardiograms will be obtained as designated in Table 6 and Table 7. Twelve-lead standard ECGs will be recorded in triplicate (1 minute apart) after subjects have been resting in the supine position for at least 5 minutes.

On any study day when ECG, vital signs, and blood samples are taken, these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.7 SAFETY MRI

Safety brain MRI assessments will be performed at the times shown in Table 6 and Table 7. Additional safety MRI scans can be performed at unscheduled visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Safety MRIs will be acquired using a standardized procedure that will include fluid-attenuated inversion recovery (FLAIR), gradient-echo, T1, and diffusion-weighted sequences to determine the presence of focal lesions including, but not limited to, evidence for ischemic and hemorrhagic stroke, subdural hematoma, neoplasm, arteriovenous malformation, micro and macrohemorrhages, superficial siderosis, lacunar infarcts, white matter abnormalities, and vasogenic edema. The imaging sequence for the Screening/safety MRI will include: T2 weighted anatomic MRI to rule out major white matter changes, cerebral infarction or other structural lesions, and a high-resolution 3D T1-weighted scan with isotropic voxels with volumes of 1 $mm^3$ or less. In addition, both FLAIR for the detection of vasogenic edema and T2* Gradient Recall Echo for the detection of microhemorrhages will be acquired. The 3D dataset will be reconstructed in transverse slices in Digital Imaging and Communications in Medicine format. The results of this MRI assessment will also be used as the Baseline Period MRI, against which changes after drug administration will be compared. Further details of the MRI protocol can be found in the Imaging Acquisition Guideline. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, and 18 and at the second Follow-Up Visit (Visit 20). In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

At any time during the treatment period, subjects will be discontinued from study drug if they develop any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. All of these features must be reported as study specific AEs (or AEs of special interest). These subjects will undergo an ED Visit within 7 days after discontinuation and Follow-Up Visits at 4 weeks and 12 weeks after the last dose of treatment. Subjects will also undertake an Unscheduled Visit (with MRI) at approximately 30 days after the visit at which such MRI features were first

identified. Additional visits may be arranged if clinically indicated in the opinion of the investigator, and may occur later than 12 weeks after the final dose of study drug.

#### 9.5.1.5.8 DERMATOLOGICAL ASSESSMENT

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at the times shown in Table 6 and Table 7. These assessments will specifically include evaluation of any areas of depigmentation or any rash.

In addition, subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregiver or informants will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or infection, and the investigator will be required to review such AEs as soon as possible and consider an unscheduled physical and dermatological evaluation. Detailed characteristics of any skin rashes will be captured in the clinical database. Physical examination may be undertaken where indicated. Treatment-emergent abnormal dermatological findings should be reported as AEs.

#### 9.5.1.5.9 NEUROLOGICAL EXAMINATION

Neurological examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations as shown in Table 6 and Table 7. Details of these examinations will be captured in an eCRF. The neurological examinations will monitor for new symptoms and signs which will then alert the investigator to consider new CNS pathology (especially slowly-evolving neurological conditions that may not lead to prominent symptoms). Examples of neurological signs that may indicate new CNS pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. In such a situation, the investigator should consider (but not limited to) demyelination in the differential diagnoses, and should discuss with the sponsor's medical monitor further investigations or treatment, which will be decided case by case. Neurological examinations will also include the assessment of cranial nerve function, especially the olfactory nerve. Treatment-emergent abnormal neurological findings should be reported as AEs.

#### 9.5.1.5.10 PREGNANCY TEST

At Screening, females of childbearing potential will have a serum pregnancy test. At Baseline and during the Treatment Period, urine samples will be obtained from females of childbearing potential for pregnancy tests (see Table 7).

#### 9.5.1.5.11 COLUMBIA SUICIDE SEVERITY RATING SCALE

An assessment of suicidal ideation and behavior using the C-SSRS will be performed at the designed time points in Table 6 and Table 7. A "yes" answer to Type 4 or 5 suicidal ideation or a "yes" response to any suicidal behavior queries will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

#### 9.5.1.5.12 BIOMARKER SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be used for exploratory biomarker analyses, as well as tested in the event that a subject develops AEs that warrant further investigation.

#### 9.5.1.5.13 OPHTHALMIC EXAMINATIONS

An ophthalmic examination will be conducted at Baseline (unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available). An additional examination will be conducted, if the subject experiences visual disturbances during the course of the study or is medically indicated. The ophthalmic examinations should include fundoscopy to look at the optic disc, macula and the rest of the retina, as well as an assessment of visual acuity and visual fields.

### 9.5.2 Schedule of Procedures/Assessments

#### 9.5.2.1 Schedule of Procedures/Assessments

Table 6 presents the Schedule of Procedures/Assessments for the Prerandomization Phase. Screening assessments will be organized into 4 tiers (see below and Figure 2).

Table 7 presents the Schedule of Procedures/Assessments for the Randomization Phase.

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

| Phase | Prerandomization | |
|---|---|---|
| Period | Screening | Baseline |
| Visit | 1 | 2 |
| **Procedures/ Assessments (to be completed in a maximum of 50 days)** | | |
| Informed consent (subject and caregiver or informant) | X (Tier 1) | |
| Demographics | X (Tier 1) | |
| Medical history[a] | X (Tier 1) | |
| Prior / concomitant medications[b] | X (Tier 1) | X |
| Vital signs including weight[c] | X (Tier 1) | X |
| Height | X (Tier 1) | |
| Complete physical examination | X (Tier 1) | |
| Routine physical examination | | X |
| CBB and ISLT[d] | X (Tier 1) | X |
| MMSE[d] | X (Tier 1) | X |
| CDR[d] | X (Tier 1) | X |
| FAQ[d] | X (Tier 1) | X |
| ADAS-cog14[d] | | X |
| 15-item Geriatric Depression Scale | X (Tier 2) | |
| Modified Hachinski ischemic scale | X (Tier 2) | |
| C-SSRS | X (Tier 2) | X |
| 12-lead ECG[e] | X (Tier 2) | X |
| Blood and urine for clinical laboratory tests[f] | X (Tier 2) | X |
| Blood for lymphocyte subset analyses[g] | X (Tier 2) | X |
| Blood for Ig analyses[h] | X (Tier 2) | X |
| Blood for viral screen[i] | X (Tier 2) | |
| Blood for thyroid function tests[j] | X (Tier 2) | |
| Blood for vitamin B12 test | X (Tier 2) | |
| Test for previous TB exposure | X (Tier 2) | |
| Urine drug screen | X (Tier 2) | |
| Serum pregnancy test (females of childbearing potential only) | X (Tier 2) | |
| Urine pregnancy test (females of childbearing potential only) | | X |
| Safety and Volumetric MRI[k] | X (Tier 3) | |
| Amyloid PET scan[l] | X (Tier 4) | |
| Inclusion and Exclusion criteria | X (All tiers) | X |
| Adverse events | X (All tiers) | X |
| CSF sampling for PK, PD and storage[m] | | X |
| Blood sample for PK assessments[n] | | X |
| Blood sample for PD and exploratory biomarker assessments[o] | | X |
| Blood sample for pharmacogenomics | | X |
| Blood sample for storage for immune status[p] | | X |
| Blood sample for PBMC isolation | | X |
| Blood sample for viral characterization[q] | | X |
| Centralized dermatological assessment via photography[r] | | X |
| Neurological examination[s] | | X |
| Ophthalmic assessment[t] | | X |

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

AchEI = acetylcholinesterase inhibitor, AD = Alzheimer's disease, ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CDR = Clinical Dementia Rating, CMV = cytomegalovirus, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), Ig = immunoglobulin, INR = Inernational Normalized Ratio, ISLT = International Shopping List Task (immediate and delayed recall), LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetics, PET = positron emission tomography, PT = prothrombin time, PTT = partial thromboplastin time,TB = tuberculosis.

Note: Screening assessments/procedures have been organized into 4 distinct tiers. All assessments and procedures in each tier should be completed (see Figure 2), and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 procedures may be performed on the same day as Tier 1 procedures, as long as the results of all Tier 1 procedures (eg, delayed recall on the ISLT) show that the subject is eligible to continue with screening activities. Similarly, all screening assessments and procedures must be completed, and eligibility to continue in the study confirmed, before any baseline assessments and procedures commence. Adverse events and eligibility against inclusion and exclusion criteria must be assessed at each stage within the Screening Visit and at the Baseline Visit. (revised per Amendment 01)

Note: All screening and baseline assessments are to be completed within 50 days. The interval between availability of the results of the last screening assessment (PET scan) and the first baseline (Visit 2) assessments should be as short as possible and ideally should not exceed 7 days. Visit 3 (Randomization) (see Table 7) should occur 7 to 10 days after completion of the Baseline visit (Visit 2) and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion #19 into account. Thus, the total Prerandomization Phase may be up to 60 days.

a: To include: mild cognitive impairment and AD history; history of TB, vaccination history against and infections due to varicella zoster virus (chickenpox and herpes zoster or shingles); infections due to HSV1 (orolabial herpes or cold sores) and 2 (genital herpes). Medical history of infections to include: onset, duration, relapse frequency, severity, and treatments.

b: Prior and concomitant medications include AChEIs and memantine, and other medications for cognitive decline.

c: Weight, respiratory rate, body temperature, and sitting blood pressure and heart rate will be obtained.

d: To be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). The order of assessments is: MMSE, CDR, FAQ, ISLT (immediate recall), CBB, ISLT (delayed recall), and CBB (repeat CBB for additional practice) at Screening; and MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall) at the Baseline Visit. At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

e: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

f: Clinical laboratory tests consist of hematology (including PT, PTT, and INR), clinical chemistry, and urinalysis.

g: Lymphocyte subsets to be measured include CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cells), CD16/CD56 (natural killer cells) and CD14 (macrophages). Regulatory T cells will also be measured (CD4, CD25, and CD127, FoxP3). Viability staining may also be employed.

h: Igs to be analyzed include IgG, IgA and IgM.

i: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

j: Thyroid function tests include thyroid stimulating hormone, free triidothyronine and free thyroxine.

k: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images. MRI will be read by an approved central reader. Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session. (revised per Amendment 01)

l: PET scanning will be performed with a locally approved β-amyloid imaging agent, eg, Amyvid if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. The PET image will be centrally read for the purpose of determining eligibility for inclusion into the study.

m: CSF will be collected by LP after fasting (preferred), or at least 2 hours after the most recent meal. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

observation. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 and Visit 18) can be performed at a similar time of day (±1 hour) for each individual subject. If the LP and cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. The CSF sample will be used for PK and PD assessments. A CSF sample will also be stored for testing in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection). (revised per Amendment 01)

n: The PK blood sample should be collected on the same day shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

o: The PD and exploratory biomarker blood sample should be collected shortly before or shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 01)

p: A blood sample will be collected at Baseline and stored. This sample may be used for exploratory biomarkers associated with study drug or disease, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

q: Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

r: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. See Section 9.5.1.5.8 for further details.

s: To be performed by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations. Section 9.5.1.5.9 details what is included in the neurological examination.

t: An ophthalmic examination will be conducted at Visit 2 unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available. The ophthalmic examination should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields.

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| Phase | Randomization | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Period | Treatment | | | | | | | | | | | | | | | | | Follow-Up | | |
| Visit[a] | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | ED[b] | 19[c] | 20[c] | UNS Visit[d] |
| Day | 1 | 8 | 15 | 22 | 29 | 43 | 57 | 71 | 85 | 113 | 141 | 183 | 274 | 365 | 456 | 547 | | 575 | 631 | |
| Week | 1 | 2 | 3 | 4 | 5 | 7 | 9 | 11 | 13 | 17 | 21 | 27 | 40 | 53 | 66 | 79 | | 83 | 91 | |
| Weeks elapsed since first dose | 0 | 1 | 2 | 3 | 4 | 6 | 8 | 10 | 12 | 16 | 20 | 26 | 39 | 52 | 65 | 78 | | 82 | 90 | |
| Nominal months elapsed since first dose | 0 | | | | 1 | | 2 | | 3 | 4 | 5 | 6 | 9 | 12 | 15 | 18 | | 19 | 21 | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | |
| Routine physical examination | X | | | | X | | X | | X | | | X | X | X | X | X | X | X | X[e] | X |
| Inclusion and Exclusion criteria | X | | | | | | | | | | | | | | | | | | | |
| Vital signs[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[e] | X |
| Respiratory rate | | | | | X | | X | | X | X | X | X | X | X | X | X | X | X | X[e] | X |
| Weight | | | | | | | | | X | | | X | X | X | X | X | X | | X | X |
| Centralized dermatological assessment via photography[g] | | | | | | | | | X | | | X | X | X | X | X | X | | X | X |
| Neurological examination[h] | | | | | | | | | | | | X | | X | | X | X | X | X | X |
| Ophthalmic examination[i] | | | | | | | | | | | | | | | | | | | | X |
| Concomitant medications[j] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG[k] | | | X | | X | | X | | X | | | X | | X | | X | X | X | X[e] | X |
| Clinical biochemistry and urinalysis | | | X | | X | | X | | X | | | X | X | X | X | X | X | X | X[e] | X |
| Complete blood count | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[e] | X |
| Blood samples for lymphocyte subset analyses[l] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[e] | X |
| Blood samples for Igs[m] | | | | | X | | X | | X | | | X | | X | | X | X | X | X[e] | X |
| Blood samples for isolation of PBMCs | | | X | | | | | | X | | | | | | | | | | X | |
| Urine pregnancy test (females of CBP only) | X[n] | | | | | | | | X | | | X | X | X | X | X | X | X | | X |
| Blood sample for storage for immune status[o] | | | | | X | | | | X | | | X | | X | | X | X | X | X | X |
| CBB and ISLT[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| MMSE[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| CDR[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| ADAS-cog$_{14}$[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| **Phase** | **Randomization** | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | | | | | **Follow-Up** | | |
| **Visit**[a] | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **ED**[b] | **19**[c] | **20**[c] | **UNS Visit**[d] |
| **Day** | **1** | **8** | **15** | **22** | **29** | **43** | **57** | **71** | **85** | **113** | **141** | **183** | **274** | **365** | **456** | **547** | | **575** | **631** | |
| **Week** | **1** | **2** | **3** | **4** | **5** | **7** | **9** | **11** | **13** | **17** | **21** | **27** | **40** | **53** | **66** | **79** | | **83** | **91** | |
| **Weeks elapsed since first dose** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **10** | **12** | **16** | **20** | **26** | **39** | **52** | **65** | **78** | | **82** | **90** | |
| **Nominal months elapsed since first dose** | **0** | | | | **1** | | **2** | | **3** | **4** | **5** | **6** | **9** | **12** | **15** | **18** | | **19** | **21** | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | |
| FAQ[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| C-SSRS | | | | | X | | X | | X | | | X | X | X | X | X | X | X | X[e] | X |
| Safety and Volumetric MRI[q] | | | | | | | | | | | | X | | X | | X | X | | X | X |
| Amyloid PET[r] | | | | | | | | | | | | | | | | X | X | | | |
| Telephone contact[s] | | | X | | X | | | | X | | | X | | X | | X | X | | | X |
| Blood samples for PK[t] | | | X | | X | | | | X | | | X | | X | | X | X | | | X |
| Blood samples for PD and exploratory biomarkers[u] | | | X | | X | | | | X | | | X | | X | | X | X | X | X | |
| CSF sampling for PK and PD[v] | | | | | X | | | | | | | | | | | X | X | | | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Sleep/dream questionnaire[w] | | | | | | | | | | | | | | | | | | | | X |
| Randomization | X | | | | | | | | | | | | | | | | | | | |
| Dispense study drug[x] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |

**Notes for Table 7**

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating scale, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), Ig = immunoglobulin, ISLT = International Shopping List Task, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, UNS = unscheduled.

a: Visit 3 should be conducted 7 to 10 days after completion of the Baseline visit (Visit 2) assessments and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion #19 into account. A window of ±3 days will be permitted for Visit 4 to 14 inclusive. A window of ±10 days will be permitted for Visit 15 to 18 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since first dose" at subsequent visits.

b: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 19 and Visit 20, respectively). Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie. at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB, and ISLT) will be conducted. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) after the Early Discontinuation Visit or within ± 8 days of either of the Follow-Up Visits (Visit 19 and Visit 20). Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

c: All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 19 and Visit 20 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up period.

d: Unscheduled visits may be conducted at any time that safety or safety MRI data indicate per protocol or as clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

e: Only if clinically significant abnormalities are found at Visit 19 and the investigator considers it necessary to repeat at Visit 20. However, lymphocyte subsets and Igs should be repeated at Visit 20 if they were outside of the normal range (regardless of clinical significance) at Visit 19.

f: Measurements of body temperature and sitting blood pressure and heart rate will be obtained.

g: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. Additional UNS dermatological assessments should be conducted in response to any dermatological AEs of concern, eg, depigmentation, rash, herpetic lesion.

h: Examples of neurological signs that may indicate new central nervous system pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

i: If the subject experiences visual disturbances during the course of the study, the subject will be referred to a specialist for a further ophthalmic examination, which should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields

j: Please refer to Section 9.4.7, which details prohibited and permitted medications in the study and associated timeframes.

k: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

l: Lymphocyte subsets to be measured include CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [NK cells] and CD14 [macrophages]) and total lymphocytes. Regulatory T cells will also be measured (CD4, CD25 and CD127, FoxP3). Viability staining may also be employed.

m: Igs to be analyzed include IgG, IgA, and IgM.

n: An additional assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

o: Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

p: These assessments are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The order of assessments will be: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). At visits where the CDR or FAQ are conducted, the investigator will determine whether the informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

q: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images inMRI will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, and 18 and 20. In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A volumetric MRI sequence will be collected in all subjects immediately following all safety MRI assessments. (revised per Amendment 01)

r: PET scanning will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks.

s: Site staff will contact the subject or the caregiver or informant the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the caregiver or informant, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

t: Two plasma PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visit 5, Visit 11, Visit 14 and Visit 16 and 4 to 8 hours postdose at Visit 7 and Visit 18 (or ED). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or ED) the PK blood sample should be collected shortly before or shortly after completing the LP. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected, followed by LP at approximately the same time as at previous visits. A second PK blood sample will be collected as close as possible to the LP, either shortly before or shortly after the LP. (revised per Amendment 01)

u: PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day. At Visits 5, 11, 14, and 16 the PD blood samples should be collected predose.

v: All visits at which CSF samples are scheduled to be taken also include blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Baseline LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If the LP and the cognitive tests are performed on the same day, the LP must be performed after the cognitive tests have been completed and the subject should rest and drink some fluid to hydrate before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. (revised per Amendment 01)

w: Subjects reporting adverse events relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

x: The first dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time for post-dose medical observation.

#### 9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 6 and Table 7 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 4 tiers (see Table 6, Section 9.1.1.1, and Figure 2.

See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 8 presents the number of blood and CSF samples, and the total volume of blood and CSF that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety.

**Table 8 Summary of Blood and CSF Sample Volumes**

| Assessment | Total number of collection time points | Number of time points x volume per collection (mL whole blood or CSF) | | Total volume (mL whole blood or CSF) |
|---|---|---|---|---|
| | | Screening and Baseline Periods | Treatment and Follow-Up Periods | |
| **Blood** | | | | |
| Chemistry | 12 | 2 x 2 mL | 10 x 2 mL | 24 mL |
| Hematology | 18 | 2 x 5 mL | 16 x 5 mL | 90 mL |
| Lymphocyte subset analyses | 18 | 2 x 4 mL | 16 x 4 mL | 72 mL |
| PBMC | 4 | 1 x 16 mL | 3 x 16 mL | 64 mL |
| IgA, IgM, IgG | 9 | 2 x 2 mL | 7 x 2 mL | 18 mL |
| PT, PTT for INR | 2 | 2 x 3 mL | None | 6 mL |
| Thyroid function tests (thyroid stimulating hormone, free triidothyronine and free thyroxine) | 1 | 1 x 3 mL | None | 3 mL |
| Viral screen (Hepatitis B and C) | 1 | 1 x 4 mL | None | 4 mL |
| Viral characterization | 1 | 1 x 4 mL | None | 4 mL |
| Vitamin B12 | 1 | 1 x 2 mL | None | 2 mL |
| Serum pregnancy test | 1 | 1 x 2 mL | None | 2 mL |
| Tuberculosis (interferon-gamma release assays) | 1 | 1 x 3 mL | None | 3 mL |
| Sample for immune status | 8 | 1 x 4 mL | 7 x 4 mL | 32 mL |
| PD sample | 9 | 1 x 4 mL | 8 x 4 mL | 36 mL |
| PK analysis | 7 | 1 x 3 mL | 6 x 6 mL | 39 mL |
| Pharmacogenetic sample | 1 | 1 x 3 mL | None | 3 mL |
| All blood samples, total volume whole blood collected | | 80 mL | 322 mL | 402 mL |
| **CSF** | | | | |
| PD and PK samples | 3 | 1 x 12 mL | 2 x 12 mL | 36 mL |

CSF = cerebrospinal fluid, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetic, PT = prothrombin time, PTT = partial thromboplastin time.

### 9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include vital signs, clinical laboratory assessments, physical examinations, ECG measurements, and reports of AEs. MRI will be used to detect vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage and is a standard evaluation to ensure subject safety. The C-SSRS has been endorsed by the FDA as a measure of potential suicidality (Guidance for Industry Suicidality).

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, in addition to mitigating clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. Details are provided in Section 9.2.6.

### 9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

#### 9.5.4.1 Reporting of Serious Adverse Events

**All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.**

SAEs, regardless of causality assessment, must be collected up to 3 months after the last dose of study drug, ie, through to the second follow-up visit (Visit 20). In subjects who discontinue study drug early, but continue with efficacy assessments, SAEs only need to be solicited up to 3 months after the last dose of study drug. However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

**For urgent safety issues**, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

#### 9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must discontinue study treatment.

#### 9.5.4.3 Reporting of Events Associated with Special Situations

##### 9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

| | |
|---|---|
| Overdose | Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose |
| Misuse | Intentional and inappropriate use of study drug not in accordance with the protocol |
| Abuse | Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects |
| Medication error | Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject |

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

#### 9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2) should always be considered serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

### 9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

### 9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

#### 9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

### 9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue study drug or withdraw from the study at any time for any reason. All subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 19 and Visit 20, respectively) (see Section 9.1.2.3). See Table 7 for full details of the assessments to be performed at these visits. Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie, at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog14, FAQ, CBB and ISLT) will be conducted. Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above. Subjects who discontinue study drug early (as opposed to subjects whose dosing with study drug is temporarily suspended under Medical Monitor guidance) will not be permitted to restart study drug.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and will provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who withdraw prematurely from the study will be withdrawn for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for withdrawal from the study. Study disposition information will be collected on the Subject Disposition eCRF.

A subject removed from the study for any reason may not be replaced.

### 9.5.6 Abuse or Diversion of Study Drug

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Potential Abuse-related Medication Handling Event eCRF.

### 9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

## 9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

### 9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

### 9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy assessments performed in this study.

## 9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, except for the Bayesian methods on the primary endpoint.

### 9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the statistical analysis plan, which will be finalized before the first interim efficacy analysis.

#### 9.7.1.1 Study Endpoints

See Section 9.2.3 for a discussion of the rationale for the selection and clinical relevance of the primary study endpoint. Further information on the derived ADCOMS is described in Section 9.5.1.3.1.

##### 9.7.1.1.1 PRIMARY ENDPOINT

- Change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects

##### 9.7.1.1.2 SECONDARY ENDPOINTS

Change from baseline in:

- Total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- CSF Aβ(1-x) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
- The derived ADCOMS at 18 months of treatment in mild to moderate AD subjects (revised per Amendment 01)

#### 9.7.1.1.3 EXPLORATORY ENDPOINTS

(revised per Amendment 01)

Change from baseline in:

- The derived ADCOMS at 12 months of treatment in MCI/Prodromal and mild to moderate AD subjects
- Total hippocampal volume at 12 and 18 months of treatment in mild to moderate AD subjects as measured by vMRI
- CSF Aβ(1-42) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
- CSF Aβ(1-x) and Aβ(1-42) after 4 weeks and 18 months of treatment in mild to moderate AD subjects
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ in MCI/Prodromal and mild to moderate AD subjects
- CSF biomarkers of neurodegeneration (eg, tau and p-tau) at 18 months of treatment in MCI/Prodromal and mild moderate AD subjects
- Plasma and CSF amyloid, and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild moderate AD subjects
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and, 18 months in MCI/Prodromal and mild to moderate AD subjects as measured by vMRI
- Brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- The population PK parameters of E2609 including the effect of intrinsic and extrinsic factors (including *NAT2* phenotype) in MCI/Prodromal and mild to moderate AD subjects

### 9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol (PP) Analysis Set is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.

- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

#### 9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: The number (percent) of randomized and treated subjects who completed the study and who withdrew from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and withdrew from the study. The primary reasons for discontinuation from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

Completion of Study Treatment: The number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for discontinuation from the study drug are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, inadequate therapeutic response, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

#### 9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, MMSE and FAQ; categorical variables include sex, age group (≤65 years, age >65 years), race, ethnicity, *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal AD or mild to moderate AD). (revised per Amendment 01)

#### 9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up period will also be recorded.

#### 9.7.1.6 Efficacy Analyses

***The MCI/Prodromal Cohort***

The study in the MCI/Prodromal cohort is based on Bayesian adaptive design. Frequent interim analyses will be performed to assess the probability of early success and futility and to make early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis. Key definitions relevant to the Bayesian aspects of the adaptive design are given below.

**Study Definitions**

- **Maximum Effective Dose ($d_{Max}$):** The dose that achieves the greatest treatment effect.
- **$ED_{90}$:** The lowest dose that achieves at least 90% of the $d_{Max}$ treatment effect in the derived ADCOMS.
- **Early Success:** The study in the MCI/Prodromal cohort will meet early success criteria if the probability that the $ED_{90}$ at 18 months of treatment achieves 25% improvement over placebo is at least 80%. Early success is achieved before all MCI/Prodromal subjects complete 18 months of treatment and can only be determined after at least 200 MCI/Prodromal subjects have been randomized. If early success is declared before full randomization, the randomization of new MCI/Prodromal subjects will stop but subjects already randomized into the study will receive the full 18 months of treatment (following confirmation from the Sponsor's Senior Management).
- **Futility:** The study in the MCI/Prodromal cohort will meet statistical futility criteria if the probability that the $ED_{90}$ is better than placebo by the clinically significant difference of 25% is less than 5% at 18 months of treatment. The statistical futility boundary is binding; if the statistical futility boundary is crossed the study will be considered to have failed.

- **Study Success:** The study in the MCI/Prodromal cohort will be considered a success if an $ED_{90}$ at 18 months treatment has at least an 80% probability of achieving 25% improvement over placebo at either an interim analysis or at the final analysis.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

All mild to moderate AD subjects will be included in the efficacy evaluations of the Mild to Moderate AD cohort. The analysis of the Mild to Moderate AD cohort is based on the group sequential design. Interim analyses in the Mild to Moderate AD cohort will only be performed after the MCI/Prodromal cohort crosses the early success boundary. The early efficacy signal based on the change from baseline of ADCOMS at 18 months is defined as crossing the interim-analysis boundaries for overwhelming efficacy in the mild to moderate AD population. The O'Brien-Fleming (OF) boundaries based on Lan-DeMets alpha spending function will be used to assess overwhelming efficacy. The corresponding OF boundaries based on *P* values will be 0.076, 0.0221, and 0.0423 for the first, second, and final analyses, respectively, according to 2 planned interim analyses at the 60% and 80% information fraction. (revised per Amendment 01)

#### 9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

***Primary analysis of primary endpoint***

The primary analysis will be based on MCI/Prodromal subjects from the FAS with the prespecified censoring rule applied. The primary endpoint is the change from baseline to 18 months in the derived ADCOMS. The dose-response of the primary endpoint is modelled with a first-order normal dynamic linear model, where Normal and Inverse-Gamma priors are used. The primary efficacy analysis will calculate the Bayesian posterior probability that the dose identified is the most likely $ED_{90}$ dose that achieves 25% improvement over the placebo arm. At each interim analysis and the final analysis, 2 Bayesian probabilities will be summarized for each active dose: the probability it is the $ED_{90}$ dose and the probability of achieving 25% improvement over the placebo arm.

For the clinical efficacy data (ie, derived ADCOMS, MMSE, CDR, ADAS-cog, CBB, ISLT, and FAQ) subjects will be censored at the time of initiation of treatment with AChEIs or memantine, if they were not on these medications at the time of Baseline cognitive assessment (Visit 2), and will be censored at the time of dose adjustment of AChEIs or memantine if they were already on stable treatment with these medications at the time of Baseline cognitive assessment (Visit 2). The value of the primary endpoint for censored subjects will be imputed using data up to the censoring time and Bayesian longitudinal modeling.

***Sensitivity analysis of primary endpoint***

After unblinding, the primary endpoint will be analyzed using the Bayesian methods described above as well as conventional statistical methods. The following additional Bayesian analyses will be conducted as sensitivity analyses:

- The primary endpoint will be analyzed regardless of initiation of treatment, or dose adjustment, with AChEIs or memantine using the same Bayesian analysis method as primary analysis. This is an intent-to-treat analysis without any censoring.
- In case of early success, the primary analysis as well as the above sensitivity analyses will be repeated after all subjects have completed 18 months of treatment or have been lost to follow-up.

Statistical methods for the final conventional analyses will use a mixed-effects model with repeated measures (MMRM) on the change from baseline in the derived ADCOMS at 18 months. The model will include treatment groups, randomization stratification variables (the presence or absence of ongoing treatment with AChEIs or memantine or both, and *ApoE4* status), and baseline ADCOMS as covariates. Other covariates such as adjusted hippocampal volume will be studied. These analyses will be performed as sensitivity analyses on the FAS as well as the PP set and as such, no multiplicity adjustments will be made to account for the interim analyses. In case of early success, the conventional analyses will also be performed using the data collected before the interim analysis.

#### 9.7.1.6.2 SECONDARY EFFICACY ANALYSES

***The MCI/Prodromal Cohort***

An MMRM will be used to analyze the following secondary endpoints:

- Change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-x) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects. Data from early discontinuations will also be included.

Comparisons between each treatment group and placebo will be performed.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

The MMRM will be used to analyze the change from baseline of derived ADCOMS at 18 months in mild to moderate AD. If there is no treatment group-by-population interaction in the overall study, the MMRM analysis will include all subjects (MCI/Prodromal or mild to moderate AD) in the overall study. Otherwise, the MMRM analysis will only include subjects in the Mild to Moderate AD cohort. The comparison between placebo and active doses will be performed within mild to moderate AD subjects regardless of subjects included in the MMRM analysis. Dunnett's method will be used to control for multiplicity due to multiple comparisons. (revised per Amendment 01)

#### 9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

(revised per Amendment 01)

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in the derived ADCOMS at 12 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in total hippocampal atrophy at 12 and 18 months in mild to moderate AD subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-42) after 4 weeks and 18 months in MCI/Prodromal subjects. Data from early discontinuations will also be included.
- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) after 4 weeks and 18 months in mild to moderate AD subjects. Data from early discontinuations will also be included.
- Change from baseline in the clinical assessments: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in plasma and CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and 18 months as measured by vMRI in MCI/Prodromal and mild to moderate AD subjects

A linear mixed-model will be used to analyze the following exploratory endpoints:

- Change from baseline in brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in CSF biomarkers of neurodegeneration (eg, tau, p-tau) at 18 months of treatment in MCI/Prodromal and mild to moderate AD subjects

Data from early discontinuations will also be used as appropriate. Comparisons between each treatment group and placebo will be performed.

A linear mixed-model with repeated measures will be used to determine the relationship between the following endpoints:

- Change from baseline in the derived ADCOMS score and the change from baseline in biomarkers in CSF at 18 months in MCI/Prodromal and mild to moderate AD subjects
- Change from baseline in the derived ADCOMS score and change from baseline in imaging biomarkers (hippocampal, whole brain, and total ventricular volumes) at 12 and 18 months in MCI/Prodromal and mild to moderate AD subjects

*ApoE* status for heterozygous and homozygous E4 carriers will be included in the model to assess the effect of *ApoE* status in this relationship.

#### 9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

##### 9.7.1.7.1 PHARMACOKINETIC ANALYSES

The Safety Analysis Set will be used for individual E2609 concentration listings. The PK Analysis Set will be used for summaries of E2609 concentrations.

##### 9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Pharmacodynamic, PGx, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate statistical analysis plan. Please also refer to Appendix 3.

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). CSF Aβ(1-x), Aβ(1-42), t-tau, p-tau, and BACE1 will be assessed and data will be presented graphically. Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status.

Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels and exposure to E2609 in CSF will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. The PK/PD relationship between plasma PK parameters with other biomarkers may also be explored using similar methods.

Additionally, the relationship between plasma and CSF exposure to E2609 and the derived ADCOMS at 18 months, and the relationship between plasma and CSF exposure to E2609 and the change from baseline for 18 months in the ADAS-cog, the CDR, and the MMSE, will be explored graphically. Any emergent relationship will be explored through population PK/PD modeling.

Exposure-safety analyses may also be conducted.

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. The genomic DNA samples may also be stored and used as

described in Section 9.7.1.7.2. Details of PGx testing may be provided and reported separately.

#### 9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, and vital sign measurements will be summarized by treatment group using descriptive statistics.

##### 9.7.1.8.1 Extent of Exposure

The extent of exposure to study drug will be summarized as cumulative extent of exposure in 3-month intervals. The number and percent of subjects will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics in 3-month intervals. The number and percent of subjects will be presented by treatment group.

##### 9.7.1.8.2 Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 17.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and preferred term. A subject will be counted only once within an SOC and preferred term, even if the subject experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with

TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and preferred term. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

Adverse events will be summarized by the following subgroups: *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical population (MCI/Prodromal or mild to moderate AD). (revised per Amendment 01)

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

#### 9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values

(TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

Lymphocyte subsets (ie, CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages]) and regulatory T cells will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose.

Serum IgG, IgM, and IgA will be measured and summarized in the same manner as other laboratory parameters.

#### 9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

#### 9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to the end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 msec
- QTc interval >480 msec
- QTc interval >500 msec

Change from baseline in QTc interval:

- QTc interval increases from baseline >30 msec
- QTc interval increases from baseline >60 msec

#### 9.7.1.8.6 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog$_{14}$, MMSE, CDR, and CBB (see Section 9.7.1.6).

### 9.7.2 Determination of Sample Size

#### 9.7.2.1 Sample Size Rationale in the MCI/Prodromal Cohort

Primary endpoint – derived ADCOMS

The sample size and design characteristics to test the hypothesis for the primary objective based on the primary endpoint, change from baseline of the derived ADCOMS at 18 months, were determined by means of simulations. Extensive study simulations have shown that a total of 500 subjects will be sufficient to demonstrate that the most likely $ED_{90}$ dose achieves a 25% improvement over placebo with a probability of at least 80% in the interim and final analyses. There is at least a 90% probability of study success for the dose response scenarios where treatment was considered to have a clinically meaningful treatment effect. Simulations have also shown that if there is no obvious dose effect, the probability of falsely claiming superiority to placebo is at most 5%.

For each of the 4 treatment groups (3 active doses and placebo) the final number of subjects per group will differ depending on the observed interim treatment responses. The simulation plan will be an appendix to the statistical analysis plan and will present further details.

vMRI

The null hypothesis is that there is no difference between active dose and placebo. There are 3 null hypotheses corresponding to 3 active doses. The alternative hypothesis is that at least 1 null hypothesis is false (1-sided). The null hypotheses will be tested using Dunnett's method with 1-sided alpha of 0.05. The statistical power was estimated through simulation for a moderate dose-response assumption that the percent reduction in change from baseline of total hippocampal volume compared with placebo would be 15%, 20%, and 25% corresponding to the 3 doses, respectively. The estimated power for the actual planned study sample size is 78% at 18 months assuming an attrition rate of 20% at 18 months. Under a stronger dose-response assumption (ie, the percent reduction in change from baseline of total hippocampal volume compared with placebo is twice as much as that in the moderate dose-response assumption), the estimated power is at least 99% at 18 months.

Amyloid PET

The null and alternative hypotheses and the statistical test are the same as those for vMRI. To estimate the sample size for the amyloid PET imaging subgroup at 18 months, a common SD of the change from baseline was estimated at 0.33 and a reasonable mean difference between treatment and placebo was estimated as 0.25 (standardized uptake value ratio [SUVR]). Assuming a moderate dose-response, the best dose would achieve a difference of 0.25 (SUVR) and the middle and low doses would achieve a difference of 0.2 and 0.15 (SUVR), respectively; this would require a total of 100 subjects from all 4 arms at 18 months to achieve 80% power.

#### 9.7.2.2 Sample Size Rationale for the Mild to Moderate AD Cohort (revised per Amendment 01)

ADCOMS at Month 18

The null hypothesis is that there is no difference between active dose and placebo. There are 2 null hypotheses corresponding to 2 active doses. The alternative hypothesis is that at least 1 null hypothesis is false. The null hypotheses will be tested using Dunnett's test with 2-sided alpha of 0.05 as described for the Mild to Moderate AD cohort in Section 9.7.1.6.2. The statistical power was estimated through simulation for the dose-response assumption that the percent reduction in change from baseline of ADCOMS at 18 months compared with placebo would be 33% and 50% corresponding to the 2 doses, respectively. The estimated power for the actual planned 200 mild to moderate AD subjects is approximately 80% assuming a 2-sided alpha of 0.05. (revised per Amendment 01)

### 9.7.3 Interim Analysis

An interim safety analysis will be conducted when the first 60 subjects have completed 12 weeks of treatment (or discontinue study drug early) in Stage A. (revised per Amendment 01)

***The MCI/Prodromal Cohort***

The Bayesian interim analyses and response adaptive randomization will be conducted by an unblinded external independent analysis group in accordance with the protocol. Oversight of the Bayesian interim analyses and response adaptive randomization will be conducted by an independent unblinded committee that has expertise with Bayesian adaptive design in clinical studies to ensure that the response adaptive randomization process and interim analyses perform as expected. The analysis group will provide the interim analysis outcomes to the committee at each interim analysis. The committee will ensure the integrity of the interim analysis and response adaptive randomization process through review of efficacy data. In addition, the committee will act in an independent advisory capacity to monitor the Bayesian interim analysis outcomes according to the early success and futility boundaries prespecified in the protocol. The committee will not be charged with any subject safety issues; this will remain the responsibility of the DSMB.

If the predefined early success criteria are met during the recruitment period, further recruitment and enrollment of MCI/Prodromal subjects into the study will stop (following confirmation from the Sponsor's Senior Management) and all currently randomized subjects will complete the full 18 months of treatment. No further interim analyses will be conducted after achieving early success.

If the predefined threshold for futility is reached, no additional subjects will be randomized into the study and the treatment of subjects already randomized into the study will stop and the study will be declared as "failed". All subjects will be monitored for safety for 3 months following their last dose.

If neither early success nor futility is reached and the study reaches full randomization, all subjects will complete 18 months of treatment. Interim efficacy analyses will be conducted every 3 months after full randomization is reached to assess futility and early success until all subjects complete 18 months of treatment. After full randomization, all study subjects will stop treatment only in the event of futility.

The DSMB will continue to monitor the safety aspects of the study throughout Stage A and Stage B. Details will be provided in the DSMB Charter. The study may be stopped for safety at any time.

The first Bayesian adaptive interim analysis will be conducted when 100 MCI/Prodromal subjects have been randomized into the study (ie, including MCI/Prodromal subjects from Stage A and Stage B). (revised per Amendment 01) Further interim efficacy analyses will be conducted after each additional 50 MCI/Prodromal subjects have been randomized, to a maximum of 500 MCI/Prodromal subjects (ie, at 100, 150, 200, 250, 300, 350, 400, 450, 500 subjects randomized). If the study reaches full randomization, additional interim analyses will be conducted every 3 months until all subjects complete 18 months of treatment. The study will be monitored for futility at each interim analysis. Starting at the interim analysis for 200 subjects, the study will be monitored for success at each interim analysis. Each interim analysis will be conducted on data for the derived ADCOMS.

In addition, at each interim efficacy analysis, response adaptive randomization will be used to update the allocation of new subjects between placebo and active doses according to a predefined automated algorithm.

***The Mild to Moderate AD Cohort*** (revised per Amendment 01)

A group sequential design will be used for the Mild to Moderate AD cohort. (revised per Amendment 01) This design includes 3 looks, 2 interim looks (when 60% and 80% information fractions are achieved) and 1 final look. The information fraction is the number of assessments in all treatment arms divided by the total number of expected assessments. Interim analyses will be performed after the MCI/Prodromal cohort crosses the early success boundary. The corresponding efficacy boundaries will be 0.076, 0.022, and 0.0423 for the first, second, and final analyses, respectively. If the actual information fraction during the interim analyses is different from 60% or 80% at the interim, the efficacy boundaries will be adjusted based on the actual information fraction.

If early success in the MCI/Prodromal cohort is not achieved before the final analysis that is performed when all subjects have completed 18 months treatment, then only a final analysis will be performed in mild to moderate AD subjects. In the event of futility in the MCI/Prodromal cohort, an analysis will be performed for the Mild to Moderate AD cohort based on the data for mild to moderate AD subjects available at that time. (revised per Amendment 01)

Randomization into the Mild to Moderate AD cohort will remain at a fixed schedule throughout Stage B. (revised per Amendment 01)

The interim analyses in the Mild to Moderate AD cohort will be conducted by an independent analysis group. (revised per Amendment 01)

### 9.7.4 Other Statistical/Analytical Issues

**Adaptive Randomization in the MCI/Prodromal Cohort**

Randomization to placebo or 1 of 3 dose groups of E2609 will be fixed for the first 100 MCI/Prodromal subjects randomized in the study (1:1:1:1; placebo to each of the 3 active doses for the first 100 MCI/Prodromal subjects randomized, including those randomized from both Stage A and Stage B). Thereafter, randomization probabilities to each treatment group will be updated at each interim analysis, such that the randomization probability will be increased for the placebo group and dosage groups that represent the potential target dose ($ED_{90}$), and simultaneously decreased for other active arms. (revised per Amendment 01)

**Randomization in the Mild to Moderate AD Cohort** (revised per Amendment 01)

In Stage A, the mild to moderate AD subjects will be randomized to placebo or 1 of 3 E2609 dose groups (5 mg, 15 mg, and 50 mg of E2609) at a 1:1:1:1 ratio, while in Stage B, the mild to moderate AD subjects will be randomized to placebo or 1 of 2 E2609 dose groups (15 mg and 50 mg E2609) at a 1:1:1 ratio. (revised per Amendment 01)

**Stratification** (revised per Amendment 01)

Within the 2 clinical cohorts (MCI/Prodromal and mild to moderate AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no). (revised per Amendment 01)

### 9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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# 11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

## 11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

## 11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

## 11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

## 11.4 Recording of Data

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document, except when a section of the eCRF itself is used as the source document. Any correction to entries made on the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each eCRF. The investigator will report the eCRFs to the sponsor and retain a copy of the eCRFs.

## 11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents.

## 11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

## 11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

## 11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

## 11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

## 11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or CTA executed between the institution/investigator and the sponsor/CRO.

## 11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

## 11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

# 12 APPENDICES

## Appendix 1 Sponsor's Grading for Laboratory Values

(revised per Amendment 01)

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **BLOOD/BONE MARROW** | | | | |
| Hemoglobin (conversion from g/dL×0.6206) | **Female** (ULN=15.9 g/dL)<br><11.1 – 10.0 g/dL<br><111 – 100 g/L<br><6.9 – 6.2 mmol/L<br>**Male** (ULN=17.7 g/dL)<br><12.6 – 10.0 g/dL<br><126 – 100 g/L<br><7.8 – 6.2 mmol/L | <10.0 – 8.0 g/dL<br><100 – 80 g/L<br><6.2 – 4.9 mmol/L | <8.0 g/dL<br><80 g/L<br><4.9 mmol/L;<br>transfusion indicated | life-threatening consequences; urgent intervention indicated |
| Leukocytes (total white blood cell) | <3.40 – 3.0×$10^9$/L<br><3.40 $10^3$/uL – 3000/$mm^3$<br>(ULN=10.80 $10^3$/μL) | <3.0 – 2.0×$10^9$/L<br><3000 – 2000/$mm^3$ | <2.0 – 1.0×$10^9$/L<br><2000 – 1000/$mm^3$ | <1.0×$10^9$/L<br><1000/$mm^3$ |
| Lymphocytes | not applicable | <700 – 500/$mm^3$<br><0.7 – 0.5×$10^9$/L | <500 – 200/$mm^3$<br><0.5 – 0.2×$10^9$/L | <200/$mm^3$<br><0.2×$10^9$/L |
| Neutrophils | not applicable | <1.4 – 1.0×$10^9$/L<br><1400 – 1000/$mm^3$ | <1.0 – 0.5×$10^9$/L<br><1000 – 500/$mm^3$ | <0.5×$10^9$/L<br><500/$mm^3$ |
| Platelets | <155 – 75.0×$10^9$/L<br><155 $10^3$/uL – 75,000/$mm^3$<br>(ULN=379 $10^3$/μL) | <75.0 – 50.0×$10^9$/L<br><75,000 – 50,000/$mm^3$ | <50.0 – 25.0×$10^9$/L<br><50,000 – 25,000/$mm^3$ | <25.0×$10^9$/L<br><25,000/$mm^3$ |
| **METABOLIC/LABORATORY** | | | | |
| Albumin, serum- low (hypoalbuminemia) | **2 - 59 years** (ULN=5.5 g/dL)<br><3.5 – 3 g/dL<br><35 – 30 g/L<br>**59 -69 years** (LLN-ULN)<br><3.6 g/dL – 3 g/dL<br>**69 -79 years** (LLN-ULN)<br><3.5g/dL – 3g/dL<br>**79 -89 years** (LLN-ULN)<br><3.5g/dL – 3g/dL | <3 – 2 g/dL<br><30 – 20 g/L | <2 g/dL<br><20 g/L | life-threatening consequences; urgent intervention indicated |
| Alkaline phosphatase | **Female:**<br>**18 -19 years**<br>>101 – 3.0×101<br>**19 -61 years**<br>ULN=107<br>**61 -71 years**<br>ULN=112<br>**71 -150 years**<br>ULN=108<br>**Male**<br>**18 -19 years**<br>>127 – 3.0×127<br>**19 -61 years**<br>ULN=102<br>**61 -71 years**<br>ULN=103<br>**71 -150 years**<br>ULN=105 | >3.0 – 5.0×ULN<br>See previous column for ULN values | >5.0 – 20.0×ULN<br>See previous column for ULN values | >20.0×ULN<br>See previous column for ULN values |
| Alanine aminotransferase | **Female:**<br>>32 – 3.0×32<br>**Male:**<br>>44 – 3.0 x 44 | **Female:**<br>>3.0 – 5.0×32<br>**Male**<br>>3.0 – 5.0×44 | **Female:**<br>>5.0 – 20.0×32<br>**Male:**<br>>5.0 – 20.0×44 | **Female:**<br>>20.0×32<br>**Male:**<br>>20.0×44 |
| Aspartate aminotransferase | >40 – 3.0×40 | >3.0 – 5.0×40 | >5.0 – 20.0×40 | >20.0×40 |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Bilirubin (hyperbilirubinemia) | >1.2 – 1.5×1.2 | >1.5 – 3.0×1.2 | >3.0 – 10.0×1.2 | >10.0×1.2 |
| Calcium, serum-low (hypocalcemia) (conversion to mmol×0.25) | <8.5 – 8.0 mg/dL<br><2.13 – 2.0 mmol/L | <8.0 – 7.0 mg/dL<br><2.0 – 1.75 mmol/L | <7.0 – 6.0 mg/dL<br><1.75 – 1.5 mmol/L | <6.0 mg/dL<br><1.5 mmol/L |
| Calcium, serum-high (hypercalcemia) | >10.6 – 11.5 mg/dL<br>>2.65 – 2.9 mmol/L | >11.5 – 12.5 mg/dL<br>>2.9 – 3.1 mmol/L | >12.5 – 13.5 mg/dL<br>>3.1 – 3.4 mmol/L | >13.5 mg/dL<br>>3.4 mmol/L |
| Cholesterol, serum-high (hypercholesterolemia) (conversion to mmol/L ×0.02586) | **0 -19 years**<br>>169 – 300 mg/dL<br>>4.37 – 7.75 mmol/L<br>**19 -150 years**<br>>199 – 300 mg/dL<br>>5.15 – 7.75 mmol/L | >300 – 400 mg/dL<br>>7.75 – 10.34 mmol/L | >400 – 500 mg/dL<br>>10.34 – 12.92 mmol/L | >500 mg/dL<br>>12.92 mmol/L |
| Creatinine | **Female**<br>>1.00 mg/dL – 1.5×1.00<br>**Male**<br>>1.27 mg/dL – 1.5×1.27 | **Female**<br>>1.5 – 3.0×1.00<br>**Male**<br>>1.5 mg/dL – 3.0×1.27 | **Female**<br>>3.0 – 6.0×1.00<br>**Male**<br>>3.0 mg/dL – 6.0 ×1.27 | **Female**<br>>6.0×1.00<br>**Male**<br>>6.0×1.27 |
| Gamma glutamyl transpeptidase | **Female**<br>>60 IU/L – 3.0×60<br>**Male**<br>>65 IU/L – 3.0×65 | **Female**<br>>3.0 – 5.0×60<br>**Male**<br>>3.0 – 5.0×65 | **Female**<br>>5.0 – 20.0×60<br>**Male**<br>>5.0 – 20.0×65 | **Female**<br>>20.0×60<br>**Male**<br>>20.0×65 |
| Glucose, serum-high (hyperglycemia) (conversion to mmol/L ×0.0555) | **Fasting glucose value**<br>>99 – 160 mg/dL<br>>5.5 – 8.9 mmol/L | **Fasting glucose value**<br>>160 – 250 mg/dL<br>>8.9 – 13.9 mmol/L | >250 – 500 mg/dL;<br>>13.9 – 27.8 mmol/L;<br>hospitalization indicated | >500 mg/dL;<br>>27.8 mmol/L;<br>life-threatening consequences |
| Glucose, serum-low (hypoglycemia) | <65 – 55 mg/dL<br><3.6 – 3.0 mmol/L | <55 – 40 mg/dL<br><3.0 – 2.2 mmol/L | <40 – 30 mg/dL<br><2.2 – 1.7 mmol/L | <30 mg/dL<br><1.7 mmol/L<br>life-threatening consequences;<br>seizures |
| Phosphate, serum-low (hypophosphatemia) (conversion to mmol/L ×0.323) | not applicable | <2.5 – 2.0 mg/dL<br><0.8 – 0.6 mmol/L | <2.0 – 1.0 mg/dL<br><0.6 – 0.3 mmol/L | <1.0 mg/dL<br><0.3 mmol/L<br>life-threatening consequences |
| Potassium, serum-high (hyperkalemia) | not applicable | >5.5 – 6.0 mmol/L | >6.0 – 7.0 mmol/L<br>hospitalization indicated | >7.0 mmol/L<br>life-threatening consequences |
| Potassium, serum-low (hypokalemia) | <3.5 mEq/L – 3.0 mmol/L | <LLN – 3.0 mmol/L;<br>symptomatic; intervention indicated | <3.0 – 2.5 mmol/L<br>hospitalization indicated | <2.5 mmol/L<br>life-threatening consequences |
| Sodium, serum-high (hypernatremia) | >144 mEq/L – 150 mmol/L | >150 – 155 mmol/L | >155 – 160 mmol/L<br>hospitalization indicated | >160 mmol/L<br>life-threatening consequences |
| Sodium, serum-low (hyponatremia) | <134 mEq/L – 130 mmol/L | Not applicable | <130 – 120 mmol/L | <120 mmol/L<br>life-threatening consequences |
| Triglyceride, serum-high (hypertriglyceridemia) | 150 – 300 mg/dL<br>1.71 – 3.42 mmol/L | >300 – 500 mg/dL<br>>3.42 – 5.7 mmol/L | >500 – 1000 mg/dL<br>>5.7 – 11.4 mmol/L | >1000 mg/dL<br>>11.4 mmol/L<br>life-threatening consequences |
| Uric acid, serum-high (hyperuricemia) | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | Not applicable | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | >10 mg/dL<br>>0.59 mmol/L<br>life-threatening consequences |

LLN = lower limit of normal, ULN = upper limit of normal.

## Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, Listing 3, Listing 4, Listing 5, and Listing 6. Medications permitted with restrictions are listed in Listing 7, Listing 8, and Listing 9. **These may not be all-inclusive listings.** Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-202 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 9 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

## Prohibited Prior/Concomitant Medications

### Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Prohibited from 14 days (or 5 half-lives, whichever is longer) before Randomization until after the last treatment visit** | | |
| **Anti-arrhythmic/ abnormal heart rhythm** | | |
| Amiodarone | Cordarone; Pacerone | Incidence in females greater than males, Torsades de Pointes risk regarded as low |
| Disopyramide | Norpace | Incidence in females greater than males |
| Dofetillide | Tikosyn | |
| Ibutilide | Corvert | Incidence in females greater than males |
| Procainamide | Pronestyl; Procan | |
| Quinidine | Cardioquin; Quinaglute | Incidence in females greater than males |
| Sotalol | Betapace | Incidence in females greater than males |
| **Antihistamine/ allergic rhinitis** | | |
| Astemizole | Hismanal | No longer available in United States |
| Terfenadine | Seldane | No longer available in United States |
| **Anti-anginal/ heart pain** | | |
| Bepridil | Vascor | Incidence in females greater than males |
| **Antibiotic/ bacterial infection** | | |
| Clarithromycin | Blaxin | |
| Moxifloxacin | Avelox | |
| Sparfloxadin | Zagam | |
| **Listing 1 continued** | | |
| **Antimalarial/ malaria infection** | | |
| Chloroquine | Aralen | |
| Halofantrine | Halfan | Incidence in females greater than males |
| **Antipsychotic/ anti-emetic/ schizophrenia/ nausea** | | |
| Chloropromazine | Thorazine | |
| **Gastrointestinal stimulant/ heartburn** | | |
| Cisapride | Propulsid | |
| **Antinausea/ nausea** | | |
| Domperidone | Motillum | Not available in the United States |

## Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Sedative; antinausea/ anesthesia adjunct, nausea** | | |
| Droperidol | Inapsine | |
| **Antibiotic; gastrointestinal stimulant/ bacterial infection; increase gastrointestinal motility** | | |
| Erythromycin | Erythrocin; E.E.S. | Incidence in females greater than males |
| **Antipsychotic/ schizophrenia** | | |
| Haloperidol | Haldol | When given intravenously or at higher than recommended doses, risk of sudden death, QT prolongation, and torsades increases |
| Mesoridazine | Serentil | |
| Thioridazine | Mellaril | |
| **Opiate agonist/ pain control, narcotic dependence** | | |
| Levomethadyl | Orlaam | |
| Methadone | Methadose; Dolophine | Incidence in females greater than males |
| **Anti-infective/ pneumocystis pneumonia** | | |
| Pentamidine | Pentam; NebuPent | Incidence in females greater than males |
| **Antipsychotic/ Tourette's tics** | | |
| Pimozide | Orap | Incidence in females greater than males |
| **Antilipemic/ hypercholesterolemia** | | |
| Probucol | Lorelco | No longer available in United States |
| **Anticancer** | | |
| Arsenic trioxide | Trisenox | Used for leukemia |
| Vandetanib | Zactima | Used for thyroid cancer |

Note: This list is not exhaustive.
QTc = Corrected QT interval.

## Listing 2 Prohibited Medications Within 7 Days (or 5 Half-lives, Whichever is Longer) Before Randomization and Until after the Last Treatment Visit)

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Anticoagulants** | |
| Adeporin | Normiflo |
| Alteplase, tPA | Activase, Cathflo Activase |
| Anisindione | Miradon |
| Antithrombin III | ATryn, Thrombate III |
| Argatroban | Argatroban |
| Bivalirudin | Angiomax |
| Dabigatran | Pradaxa |
| Dalteparin | Fragmin |
| Danaparoid | Orgaran |
| Dicumarol | Dicumarol |
| Enoxaparin | Lovenox |
| Fondaparinux | Arixtra |
| Heparin Sodium | Monoject |
| Lanoteplase | Lanoplase |
| Lepirudin | Refludan |
| Pentosan polysulfate sodium | Elmiron |
| Reteplase | Retavase, Retevase |
| Staphylokinase | Eskinase, Heberkinasa Kabikinase, Streptase, Thrombosolv, Zykinase |
| Streptokinase | Streptase |
| Tenecteplase | TNKase |
| Tinzaparin | Innohep |
| Urokinase | Abbokinase, Kinlytic |
| Warfarin | Coumadin, Jantoven |
| **Antiplatelet drugs** | |
| Aspirin and Plavix (revised per Amendment 01) | Aspirin or clopidogrel is permitted in all subjects. Aspirin and clopidogrel in combination is not permitted (revised per Amendment 01) |

Note: This list is not exhaustive.

## Listing 3 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Randomization and Until after the Last Treatment Visit

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Systemic Immunosuppressants[a] and Immunomodulatory therapy** | |
| Azathioprine | Azasan, Imur |
| Ciclosporine | Gengraf, Neoral |
| Dexamethasone | Decadron, Dexasone, Diodex, Hexadrol, Maxidex |
| Fingolimod | Gilenya |
| Methotrexate | Trexall |
| Methylprednisolone | Medrol, Meprolone |
| Mycophenolate | CellCept, Myfortic |
| Prednisolone | Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS |

Note: This list is not exhaustive.

a: Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

## Listing 4 Prohibited Medications Within 6 Months Before Randomization

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Immunoglobulin therapy** | |
| Adalimumab | Humira |
| Bevacizumab | Avastin |
| Efalizumab | Raptiva |
| Etanercept | Enbrel |
| Immune globulin IV, IVIG, IGIV | Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S |
| Infliximab | Remicade |
| Omalizumab | Xolair |
| Ranibizumab | Lucentis |
| Other monoclonal antibodies not listed here | |

Note: This list is not exhaustive.

### Listing 5 Prohibited Live Vaccines Within 3 Months Before Randomization Until after the Last Treatment Visit (this does not apply to non-live/inactivated vaccines)

| **Bacterial vaccines** | **Viral vaccines** |
|---|---|
| Bacillus Calmette-Guérin vaccine against tuberculosis | Measles vaccination |
| Cholera vaccination (oral) | Rubella vaccination |
| | Oral polio vaccination (Sabin) |
| | Yellow fever vaccination |
| | Varicella (chickenpox) vaccination |
| | Rotavirus vaccination |
| | Japanese encephalitis vaccination |
| | Live attenuated influenza vaccine (FluMist, Fluenz) |
| Typhoid vaccination (oral) | Mumps vaccination |

Note: This list is not exhaustive

## Listing 6 Strong CYP3A4 Inhibitors Prohibited Within 5 Half-Lives or 14 Days (Whichever Is Longer) Before Randomization Until After the Last Treatment Visit

| Generic name | Brand name(s) |
|---|---|
| boceprevir | Victrelis |
| clarithromycin | Clarithromycin, clarithromycin extended release, Prevpac |
| cobicistat | Tybost, Stribild, |
| conivaptan | Vaprisol |
| danoprevir | |
| elvitegravir | Vitekta, Stribild |
| indinavir | Crixivan |
| itraconazole | Sporanoz, Onmel |
| ketoconazole | Xolegel, Nizoral, Ketodan |
| lopinavir | Kaletra |
| nefazodone | Serzone |
| nelfinavir | Viracept |
| posaconazole | Noxafil |
| ritonavir | Norvir, Kaletra |
| saquinavir | Invirase, Fortovase |
| telaprevir | Incivek |
| telithromycin | Ketek |
| tipranavir | Aptivus |
| troleandomycin | Triocetin |
| voriconazole | Vfend, Voriconazole |

Note: This list is not exhaustive

## Permitted Prior/Concomitant Medications

### Listing 7 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Baseline Cognitive Assessments at Visit 2 and Remain on the Same Stable Dose from Baseline to Follow-Up Visit 2

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Cognitive Enhancers** | |
| Donepezil | Aricept |
| Galantamine | Reminyl |
| Memantine | Namenda |
| Rivastigmine | Exelon |

Note: This list is not exhaustive.

## Listing 8 Permitted Medications Used on PRN Basis Which are Not to be Used Within 72 Hours before Cognitive Testing

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Opiates** | |
| Morphine | Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol |
| **Opiate Agonists** | |
| Codeine | Codeine |
| Fentanyl | Actiq, Duragesic, Fentora, Onsolis, Sublimaze |
| Meperidine | Demerol, Meperitab |
| Oxycodone | Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol |
| Other opioids or opioid agonists which are used on PRN basis | |
| **Benzodiazepines and sedatives** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Amitriptyline | (various) |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Dothiepin | (various) |
| Estazolam | ProSom |
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |
| Lorazepam | Ativan |
| Midazolam | Versed |
| Olanzapine | Zyprexa |
| Promethazine | Phenergan; others |
| Ramelteon | Rozerem |
| Risperidone | Risperdal |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zolpidem | Ambien; others |
| Zopiclone | (various) |
| Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives | |

Note: This list is not exhaustive

PRN = Pro re nata

## Listing 9 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| If to be used on a PRN basis see Listing 8. If to be used chronically, subjects must be on a stable dose for ≥4 weeks before Baseline. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks. | |
| **Antidepressants** | |
| Amitriptyline hydrochloride | Elavil |
| Amoxapine | Amoxapine |
| Bupropion | Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin |
| Citalopram | Celexa |
| Clomipramine hydrochloride | Anafranil |
| Desipramine hydrochloride | Norpramin |
| Desvenlafaxine | Pristiq |
| Doxepin hydrochloride | Prudoxin, Silenor, Sinequan, Zonalon |
| Duloxetine | Cymbalta |
| Escitalopram | Lexapro |
| Fluoxetine | Prozac, Sarafem, Selfemra |
| Fluvoxamine | Luvox |
| Imipramine hydrochloride | Tofranil |
| Isocarboxazid | Marplan |
| Maprotiline hydrochloride | Ludiomil |
| Mirtazapine | Remeron Soltab |
| Nortriptyline hydrochloride | Aventyl, Pamelor |
| Paroxetine | Paxil, Pexeva |
| Phenelzine | Nardil |
| Protriptyline hydrochloride | Vivactil |
| Rasagiline | Azilect |
| Selegiline | EMSAM |
| Sertraline | Sertaraline, Zoloft |
| Tranylcypromine | Parnate |
| Trazodone hydrochloride | Desyrel, Oleptro |
| Trimipramine maleate | Surmontil |
| Venlafaxine hydrochloride | Effexor |

## Listing 9 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Mood Stabilizers (Listing 8 continued)** | |
| Carbamazepine | Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR |
| Lamotrigine | Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR |
| Valproic acid | Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate |
| **Antipsychotics** | |
| Acetophenazine | Tindal |
| Aripiprazole | Abilify |
| Asenapine | Saphris |
| Olanzapine | Zyprexa |
| Chlorpromazine | Thorazine |
| Haloperidol | Haloperidol, Haldol |
| Clozapine | Clozaril, Fazaclo |
| Fluphenazine | Prolixin |
| L-Methylfolate | Deplin, L-Methylfolate Calcium |
| Loxapine | Loxitane |
| Mesoridazine | Serentil |
| Perphenazine | Trilafon |
| Quetiapine | Seroquel |
| Risperidone | Risperdal |
| Thioridazine | Mellaril |
| Thiothixene | Navane |
| Trifluoperazine | Stelazine |
| **Benzodiazepines** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Estazolam | ProSom |
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |

## Listing 9 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| Lorazepam | Ativan |
| Midazolam | Versed |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zopiclone | Imovane, Zimovane |
| Zopidem | Ambien, Ambien CR, Intermezzo, Stilnox, Stilnoct, Sublinox, Hypnogen, Zolsana |

Note: This list is not exhaustive.
PRN = Pro re nata

# Appendix 3 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

## Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

## Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

### Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

### Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not

currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

# Appendix 4 AEs Indicating Signals of Possible Drug Abuse Potential

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| 1 | **Euphoric mood** | Euphoric mood |
| | | Euphoria |
| | | Euphoric |
| | | Exaggerated well-being |
| | | Excitement excessive |
| | | Feeling high |
| | | Felt high |
| | | High |
| | | High feeling |
| | | Laughter |
| 2 | **Elevated mood** | Elevated mood |
| | | Mood elevated |
| | | Elation |
| 3 | **Feeling abnormal** | Feeling abnormal |
| | | Cotton wool in head |
| | | Feeling dazed |
| | | Feeling floating |
| | | Feeling strange |
| | | Feeling weightless |
| | | Felt like a zombie |
| | | Floating feeling |
| | | Foggy feeling in head |
| | | Funny episode |
| | | Fuzzy |
| | | Fuzzy head |
| | | Muzzy head |
| | | Spaced out |
| | | Unstable feeling |
| | | Weird feeling |
| | | Spacey |
| 4 | **Feeling drunk** | Feeling drunk |
| | | Drunkenness feeling of |
| | | Drunk-like effect |
| | | Intoxicated |
| | | Stoned |
| | | Drugged |
| 5 | **Feeling of relaxation** | Feeling of relaxation |
| | | Feeling relaxed |
| | | Relaxation |
| | | Relaxed |
| | | Increased well-being |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Excessive happiness |
| 6 | **Thinking abnormal** | Thinking abnormal |
| | | Abnormal thinking |
| | | Thinking irrational |
| | | Thinking disturbance |
| | | Thought blocking |
| | | Wandering thoughts |
| 7 | **Hallucination** | Hallucination |
| | | Illusions |
| | | Flashbacks |
| | | Floating |
| | | Rush |
| | | Feeling addicted |
| 8 | **Inappropriate affect** | Elation inappropriate |
| | | Exhilaration inappropriate |
| | | Feeling happy inappropriately |
| | | Inappropriate affect |
| | | Inappropriate elation |
| | | Inappropriate laughter |
| | | Inappropriate mood elevation |
| 9 | **Mood disorders and disturbances** | Mental disturbance |
| | | Depersonalisation |
| | | Psychomotor stimulation |
| | | Mood disorders |
| | | Emotional and mood disturbances |
| | | Delirium |
| | | Delirious |
| | | Mood altered |
| | | Mood alterations |
| | | Mood instability |
| | | Mood swings |
| | | Emotional lability |
| | | Emotional disorder |
| | | Emotional distress |
| | | Personality disorder |
| | | Impatience |
| | | Abnormal behavior |
| | | Delusional disorder |
| | | Irritability |
| 10 | **Drug tolerance** | Drug tolerance |
| | | Habituation |
| | | Drug withdrawal syndrome |
| | | Substance-related disorders |
| 11 | **Psychosis** | Psychosis |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Psychotic episode or disorder |
| 12 | **Dissociative State** | Dissociation |
| | | Disconnected |
| | | Derealisation |
| | | Depersonalisation |
| | | Detached |
| | | Sensation of distance from one's environment |
| | | Loss of a sense of personal identity |

# PROTOCOL SIGNATURE PAGE

**Study Protocol Number:** E2609-G000-202
**Study Protocol Title:** A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability and Efficacy of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01)
**Investigational Product Name:** E2609
**IND Number:** 109308
**EudraCT Number:** 2014-002723-94

**SIGNATURES**
Authors:

PPD

PPD Neuroscience and General Medicine Product Creation Unit
Eisai Ltd.

Date

PPD

PPD Neuroscience and General Medicine Product Creation Unit
Eisai Ltd.

Date

PPD

Neuroscience and General Medicine Product Creation Unit
Eisai Inc.

Date

# INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability and Efficacy of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease (revised per Amendment 01) |
| **Investigational Product Name:** | E2609 |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

| Investigator | Signature | Date |
|---|---|---|

# REVISION HISTORY

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Revisions to grammar, spelling, etc. | Compliance with current company style guide and for general consistency | • Throughout protocol |
| Revisions made per new company protocol template | Alignment with current Eisai template | • Synopsis - Inclusion/Exclusion Criteria<br>• Section 9.1.2.3<br>• Section 9.3.1<br>• Section 9.3.2<br>• Section 9.5.1 (related subsections)<br>• Section 9.5.4<br>• Section 9.5.4.1<br>• Section 9.5.4.2<br>• Section 9.5.4.3 |
| Clarified classification of MCI due to AD | Clarification that MCI due to AD population will also be consistent with the research criteria for Prodromal AD in that impaired episodic memory is required and will be tested using a list learning task (the International Shopping List Task) | • Synopsis – Study Design<br>• Section 9.1 |
| Replaced "enroll" with "randomize," pertaining to subject entry into study | Correction to terminology | • Synopsis – Study Design<br>• Section 9.1<br>• Section 9.3 |
| Added criterion excluding subjects with hepatic impairment and total bilirubin greater than 1.5×ULN or INR greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded. | At request of FDA, exclude subjects who have hepatic impairment | • Synopsis – Inclusion/Exclusion Criteria<br>• Abbreviation List<br>• Section 9.3.2 |
| Added coagulation parameters for prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR) to screening and baseline procedures | Screen for hepatic impairmnent | • Synopsis – Inclusion/Exclusion Criteria<br>• Abbreviation list<br>• Section 9.3.2<br>• Table 4<br>• Table 6<br>• Table 8 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| For subjects who discontinue study drug prematurely, conduct efficacy assessments postdose at same time points as subjects who continue in the study. Added FAQ to this set of efficacy assessments. | To facilitate efficacy analyses, which are based on longitudinal modeling for all subjects | • Synopsis –Study Design<br>• Section 9.1.2.2<br>• Section 9.3.3<br>• Section 9.5.4.1<br>• Section 9.5.5<br>• Table 7 |
| Delete diagram of E2609 structure | This display is not needed for the protocol. The Investigator's Brochure has this information. | • Section 9.4.2.1 |
| Additional blood samples to be taken at Visits 19 and 20 | Samples are to be put in storage to allow for assessment of immune status at end of study, as needed. | • Synopsis - Assessments<br>• Table 8 |
| Add subheadings to Section 9.7 describing the primary endpoint analysis, and text clarifying that no multiplicity adjustments will be done to account for the interim analyses | To distinguish clearly the primary analysis and the sensitivity analyses of the primary endpoint | • Synopsis - Efficacy Analyses<br>• Section 9.7.1.6.1 |
| Clarification of PK sampling upon Early Discontinuation | Additional operational details of the timing of the PK sampling at the ED visit provided | • Section 9.5.1.4.1<br>• Table 7 |
| Clarification of ApoE testing | Clarification that the ApoE genetic testing will be for homozygous or heterozygous E4, versus non-E4 | • Section 9.5.1.4.2 |
| Revision to PK/PD interim analysis text | Confirm that interim PK/PD analysis will be conducted by an independent group | • Section 9.4.6 |
| Addtion of text regarding safety signals with E2609 | To provide information on safety-driven dose adjustments | • Synopsis – Study Design<br>• Section 9.1 |
| Addition of PBMC collection/assessment at Baseline, during treatment, and posttreatment | Recent animal studies have shown an effect of E2609 on this model so they will be added to the 202 clinical study as an additional exploratory assessment. | • Synopsis – Safety Assessments<br>• Section 9.2.6<br>• Section 9.5.1.5<br>• Table 4<br>• Table 6<br>• Table 7<br>• Table 8 |
| Stipulate that exploratory biomarker analyses may be conducted using blood or CSF samples that may have been drawn for other purposes | To allow more flexibility for possible exploratory biomarker studies associated with study drug or disease, including miRNA and DNA | • Synopsis - Assessments,<br>• Abbreviation list<br>• Section 9.5.1.4.2<br>• Section 9.5.1.5.12<br>• Table 6<br>• Table 7 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Prohibit concomitant medications that are strong CYP3A4, inhibitors, but clarify that no restrictions are needed for other CYP3A4 inhibitors, CYP3A4 inducers, or CES2 inhibitors | At request of FDA, in light of finding that inhibition of CYP3A4 by a reference agent increases plasma levels of E2609 | • Synopsis - Concomitant Drug/Therapy<br>• Section 7.1<br>• Section 9.4.7<br>• Appendix 2(Listing 6) |
| Addition of tests for viral characterization at Baseline | To confirm by serology information of subjects prior exposure to common viruses pre-dosing with study drug | • Section 9.5.1.2.2<br>• Table 4<br>• Table 6<br>• Table 8 |
| Use of a centralized dermatologist assessment via photography | A centralized approach, using standardized photography, to FDA-required serial dermatological assessments will be employed for consistency of assessments between sites and for consistency of longitudinal assessments of individual subjects. | • Synopsis – Safety Assessments<br>• Section 9.2.6<br>• Section 9.5.1.5<br>• Section 9.5.1.5.8<br>• Table 6<br>• Table 7 |
| Removal of testing for benzodiazepines or opioids as part exclusion criteria #35 | To differentiate appropriate medicinal use from recreational drug use or abuse | • Synopsis – Exclusion Criteria<br>• Section 9.3.2 |
| Addition of analysis of other covariates such as adjusted hippocampal volume will be studied | Hippocampal volume has been shown to correlate with rate of cognitive decline and as such is a key covariate to be used in the analyses. | • Synopsis – Analysis of Primary Endpoint<br>• Section 9.7.1.6.1 |
| Addition of clarifications to ophthalmic examination | To provide more detail around the requirements for the ophthalmic exam | • Synopsis – Safety Assessments<br>• Section 9.5.1.5.13<br>• Table 6<br>• Table 7 |
| Addition of details regarding specific method of CSF collection (ie, gravity drip) | Use of materials required for suction method when collecting CSF can affect the PD data and so it is important to make it clear that only the gravity drip method can be used for collecting CSF in this study for protecting the quality and the consistency of the CSF PD data. | • Section 9.5.1.3.3<br>• Section 9.5.1.4.2<br>• Table 6<br>• Table 7 |
| Addition of specific testing for B12 levels at Screening | Abnormally low serum vitamin B12 levels are exclusionary for the study (excl criterion 8) but a blood draw for Vit B12 was inadvertently missed out of Table 6 in protocol version 1. | • Synopsis – Exclusion Criteria<br>• Section 9.3.2<br>• Section 9.5.1.2.3<br>• Figure 2<br>• Table 6 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Addition of details regard AEs that might be signals of possible drug abuse potential | Changed terminology re: collection of additional information for AEs that might be signals of possible abuse potential. No longer use the word "narrative" in order to avoid potential confusion with standard clinical trial narratives eg, for serious adverse events, adverse events leading to withdrawal, etc. | • Synopsis – Safety Assessments<br>• Section 9.2.6<br>• Section 9.5.1.5.1<br>• Appendix 4 |
| Addition of clarification regarding position for taking vital signs (ie, supine) | The American Heart Association guidelines only mention supine, standing, and sitting as positions for taking HR and BP measurements. Therefore, have changed required position from semi-supine to sitting. | • Section 9.5.1.5.4<br>• Table 6<br>• Table 7 |
| Stipulated that study drugs are to be taken with food | For consistency of treatment conditions | • Section 9.5.1.4.1 |
| Change to list of Study Specific AEs which should be considered SAEs | Eisai's standard procedures have changed such that non-serious study specific adverse events of interest are no longer reported to Eisai Product Safety; instead, any additional information required for such non-serious adverse events will be obtained through other methods. In addition, certain events (new onset seizures, ocular herpes) are now to be classified as serious as important medical events, regardless of whether they meet standard ICH serious criteria. | • Section 9.5.1.5.1<br>• Section 9.5.1.5.2 |
| Increased blood volume for PK | To match collection tubes and ensure sufficient sample for planned assays | • Table 8 |
| Corrected error in definition of PK analysis set | For accuracy | • Synopsis – Study Endpoints<br>• Section 9.7.1.2 |

## Revisions to Version 1.0

## New version/date: Version 2.0, 21 Oct 2014

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Addition of details regarding discontinuation of study drug | To clearly and consistently differentiate "discontinuation from study drug" from "withdrawal from study" | • Synopsis<br>• Section 7<br>• Section 9.1.2.1<br>• Section 9.2.6<br>• Section 9.3.3<br>• Table 1<br>• Table 2<br>• Section 9.4.1<br>• Section 9.4.4<br>• Section 9.5.1.5.1<br>• Section 9.5.1.5.3<br>• Section 9.5.5 |
| Re-ordered prohibited medication lists | For consistency, all lists re-ordered in alphabetical order of generic drug name, and footnotes revised for overall consistency | • Appendix 2 |
| Moved nefazodone from Listing 9 to Listing 6 | Nefazodone is a strong CYP3A4 inhibitor and is therefore prohibited. | • Appendix 2 |

# 1 TITLE PAGE


## Clinical Study Protocol

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability, and Efficacy of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's Disease |
| **Sponsor:** | Eisai Inc.<br>155 Tice Boulevard<br>Woodcliff Lake,<br>New Jersey 07677<br>United States<br><br>Eisai Ltd.<br>European Knowledge Centre<br>Mosquito Way<br>Hatfield,<br>Hertfordshire<br>AL10 9SN<br>United Kingdom<br><br>Eisai Co., Ltd.<br>4-6-10 Koishikawa<br>Bunkyo-Ku,<br>Tokyo 112 8088<br>Japan |
| **Investigational Product Name:** | E2609 |
| **Indication:** | Alzheimer's disease |
| **Phase:** | 2 |
| **Approval Date:** | V1.0 15 Jul 2014 (original protocol)<br>V2.0 21 Oct 2014 (revised original protocol) |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |
| **GCP Statement:** | This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities. |
| **Confidentiality Statement:** | This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study. |

# 2 CLINICAL PROTOCOL SYNOPSIS

**Compound No.:**

E2609

**Name of Active Ingredient:**

*N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

**Study Protocol Title**

A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability, and Efficacy of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's Disease

**Investigators**

Stage A: Investigators in United States only

Stage B: Multinational investigators

**Sites**

Stage A: Approximately 25 sites, United States only

Stage B: Approximately 125 sites, globally

**Study Period and Phase of Development**

Stage A: Approximately 32 months and will continue and overlap with Stage B

Stage B: A maximum of 40 months from initiation of Stage B

Phase 2

**Objectives**

**Primary Objectives**

1. To evaluate the efficacy of daily dosing with 3 doses of E2609 compared with placebo by establishing the lowest effective dose that achieves 90% of the greatest treatment effect ($ED_{90}$) for E2609 on the derived Alzheimer's Disease Composite Score (ADCOMS) at 18 months of treatment in subjects with Mild Cognitive Impairment due to Alzheimer's Disease/ Prodromal Alzheimer's Disease (referred to as MCI/Prodromal throughout the protocol)
2. To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with Mild Dementia due to Alzheimer's Disease (referred to as mild AD throughout the protocol)

**Secondary Objectives**

1. To evaluate the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects, as measured by volumetric magnetic resonance imaging (vMRI)

2. To evaluate the effect of E2609 compared with placebo on amyloid β(1-x) (Aβ[1-x]) in cerebrospinal fluid (CSF) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
3. To evaluate the efficacy of E2609 compared with placebo on the derived ADCOMS at 18 months in mild AD subjects

**Exploratory Objectives**

1. To explore the effect of E2609 compared with placebo on the derived ADCOMS following 12 months of treatment in MCI/Prodromal and mild AD subjects
2. To explore the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in mild AD subjects, as measured by vMRI
3. To explore the effects of E2609 compared with placebo on Aβ(1-42) in CSF after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
4. To explore the effects of E2609 compared with placebo on Aβ(1-x) and Aβ (1-42) in CSF after 4 weeks and 18 months of treatment in mild AD subjects
5. To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during posttreatment follow-up, in MCI/Prodromal and mild AD subjects, by assessment of:
   a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
   b. The Clinical Dementia Rating (CDR) scale
   c. The Mini-Mental State Examination (MMSE)
   d. The CogState Brief Battery (CBB)
   e. The Functional Assessment Questionnaire (FAQ; also known as the Functional Activities Questionnaire)
   f. The International Shopping List Task (ISLT)
6. To explore the effects of E2609 compared with placebo on various biomarkers in MCI/Prodromal and mild AD subjects. Biomarkers to be explored include:
   a. CSF biomarkers of neurodegeneration (eg, tau, phosphorylated-tau [p-tau]) after 18 months of treatment
   b. Plasma and CSF amyloid, and CSF β-amyloid converting enzyme 1 (BACE1) measurements during 18 months of treatment and during posttreatment follow-up
   c. vMRI measurements including left and right hippocampal volume, whole brain volume and total ventricular volume at 6, 12, and 18 months of treatment and during posttreatment follow-up
   d. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)
7. To characterize the population pharmacokinetics (PK) of E2609 in MCI/Prodromal and mild AD subjects, and to examine the effect of intrinsic and extrinsic factors (including N-acetyltransferase 2 [*NAT2*] phenotype) on the PK

8. To explore the relationship between the treatment effects of E2609 on the ADCOMS and its effects on CSF amyloid, CSF BACE1, CSF tau, and vMRI in MCI/Prodromal and mild AD subjects

**Study Design**

This will be a multicenter placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild AD. A common set of inclusion criteria, consistent with the National Institute on Aging – Alzheimer's Association (NIA-AA) clinical research criteria for Mild Cognitive Impairment (MCI) due to Alzheimer's Disease (AD) or mild AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with the criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria.

The study will be conducted in 2 stages, Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 (after the first 60 randomized subjects have completed 12 weeks of treatment or have discontinued study drug early) in MCI/Prodromal subjects before expanding enrollment to include a larger population of MCI/Prodromal subjects in Stage B. In addition, during Stage B of the study, subjects with mild AD will be randomized to form a separate mild AD cohort. All MCI/Prodromal subjects will be included in the primary efficacy evaluation irrespective of whether they were recruited during Stage A or Stage B of the study. Bayesian adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B.

Both Stage A and Stage B of the study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days) includes a Screening Visit (Visit 1) and a Baseline Visit (Visit 2). All screening assessments (within 4 distinct tiers) must be completed, and eligibility to continue in the study confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

**Stage A**

Stage A will randomize 60 eligible MCI/Prodromal AD subjects at Visit 3, 1:1:1:1 to 4 treatment groups. In addition to the placebo group, 3 E2609 doses will be used to reduce CSF amyloid β levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/pharmacodynamic (PD) modeling has shown that these doses should achieve these targets when administered once daily (QD) with food, and these doses will be confirmed or adjusted based on the 4-week assessment of CSF Aβ(1-x)

During Stage A, safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the first subject is randomized during Stage A of the study, an independent data safety monitoring board (DSMB; including at least 1 immunologist) will review all safety data in an unblinded manner. The DSMB will make

recommendations to Eisai after each review as to whether any change(s) to the study are necessary. Unless the DSMB recommends otherwise, randomization of subjects into Stage A of the study will continue until 60 MCI/Prodromal subjects have been randomized and dosed.

After 60 MCI/Prodromal subjects in Stage A have completed 4 weeks of treatment, an interim analysis of the E2609 PK and PD profiles will be used to confirm the E2609 doses to be used for Stage B. If the 95% confidence interval of the mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment with a dose of E2609 does not include its intended target value (ie, 25%, 50% and 75% reductions from baseline, respectively for E2609 at 5 mg, 15 mg, and 50 mg QD), PK/PD modeling will be conducted. From this model, the new target plasma steady state concentrations of E2609 required to achieve the target levels of CSF Aβ(1-x) reduction will be estimated again. Dose adjustment for Stage B may be considered if it is possible to get closer to the new target plasma steady state concentrations of E2609 required to achieve the intended target levels of CSF Aβ(1-x) reduction than is possible with the initially planned doses, given the limitation that E2609 dose adjustments will have to be in 5-mg increments or decrements. Subjects already randomized to a dose that needs to be adjusted will be switched to the new adjusted dose and complete their treatment at this new dose.

Once 60 MCI/Prodromal subjects in Stage A have completed at least 12 weeks of treatment (or discontinued study drug early) an interim safety analysis will be conducted by Eisai and the DSMB. Subjects in Stage A will continue study drug while the DSMB reviews all the available safety data, but randomization of additional subjects will not take place (ie, recruitment into Stage B will not commence) until the safety analysis is completed by the DSMB.

If there are safety signals with one of the E2609 dose groups that would require dose adjustment, changes to dose will be reflected in an amendment to the protocol. Information on how these subjects will be handled in the primary analysis will be described in the Statistical Analysis Plan.

**Stage B**

Stage B will start after the DSMB safety review of Stage A has shown acceptable safety and tolerability of E2609 and after the doses of E2609 to be used in Stage B are confirmed. Stage B will enroll, randomize, and dose up to an additional 440 eligible MCI/Prodromal subjects. In addition, a separate cohort of approximately 200 mild AD subjects will be randomized and dosed during Stage B. Safety data from Stage B will continue to be reviewed by the DSMB (approximately every 3 months) until recruitment to the study is completed; following this the DSMB will meet approximately every 6 months.

Both population cohorts will include separate placebo groups. The MCI/Prodromal cohort will include 3 doses of E2609 (5 mg, 15 mg, and 50 mg QD) whereas the mild AD cohort will only include 2 doses of E2609 (15 mg and 50 mg QD).

Bayesian adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B. The first 40 MCI/Prodromal subjects recruited into Stage B will be randomized according to a fixed schedule (1:1:1:1; placebo: 5 mg E2609: 15 mg E2609: 50 mg E2609)

and the remaining subjects in the MCI/Prodromal cohort in Stage B will be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. The mild AD subjects will be randomized according to a fixed schedule (1:1:1 placebo; 15 mg E2609; 50 mg E2609) throughout Stage B of the study.

**Early Discontinuation**

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug. Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie, at Visits 11, 14, 15, 16, 17, and 18) if these visits have not already been performed. At these visits, only the clinical efficacy assessments (MMSE, CDR, ADAS-$cog_{14}$, FAQ, CBB and ISLT) will be conducted. Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

**Follow-Up**

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug (Visit 19) and a second 12 weeks after the last dose of study drug (Visit 20). If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the posttreatment Follow-Up period.

**Number of Subjects**

- Stage A: Approximately 250 MCI/Prodromal subjects will be screened to provide 60 randomized subjects (target of 15 subjects per treatment arm).
- Stage B: Approximately 1850 MCI/Prodromal subjects will be screened to provide up to 440 enrolled subjects. The final number of MCI/Prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. In addition, approximately 835 subjects with mild AD will be screened to provide approximately 200 randomized mild AD subjects.

**Inclusion Criteria**

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD or AD dementia and is "staged" or classified as either MCI (Stage A and Stage B) or mild dementia (Stage B only) and also complies with the following:

**Required at both Screening and Baseline:**

a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician’s observation
b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT
c. FAQ ≤20
d. MMSE ≥20

2. Amyloid positive PET image based on centralized PET scan reading
3. Male or female, age 50 to 85 years, inclusive at time of consent
4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.
5. If receiving acetylcholinesterase inhibitors (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.
6. Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization.

**Exclusion Criteria**

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or magnetic resonance imaging (MRI)
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (eg, arachnoid cysts) or brain tumors (eg, meningioma).

6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could confound the MCI/Prodromal or mild AD diagnosis or could interfere with study assessments or procedures
7. A score of ≥8 on the 15-item Geriatric Depression Scale at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the lower limit of normal (LLN) for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
12. Any contraindications to lumbar puncture for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity)
13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization
20. Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests conducted at Visit 2 (eg, MMSE, CDR, etc) must be repeated.
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.

b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).

22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below LLN and confirmed by a repeat test conducted 1 week after the initial test
23. Ig (IgG, IgA, or IgM) levels below the LLN
24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate electrocardiograms (ECGs). A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute at Screening or Baseline
29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.
33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.

36. Has a "yes" answer to the Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period and for 28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.
    - Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.
      (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

44. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or not practicing highly effective contraception throughout the study period or for 28 days after study drug discontinuation). No sperm donation is allowed during the study period or for 28 days after study drug discontinuation.

**Study Treatments**

E2609 tablets of 5-mg, 10-mg and 25-mg dose strengths will be supplied. Placebo tablets to match E2609 will be of identical appearance. Each subject will receive 2 tablets, which when combined will make up the required doses of E2609 (see below) or placebo, to be administered orally QD with food.

- MCI/Prodromal Cohort: 3 doses (5 mg, 15 mg, and 50 mg) of E2609 or placebo
- Mild AD Cohort: 2 doses (15 mg and 50 mg) of E2609 or placebo.

**Duration of Treatment**

The maximum duration of a subject's participation in the study will be approximately 2 years, comprising:

- Screening and Baseline Periods (Prerandomization Phase): up to 60 days

(In subjects who have an active infection within 4 weeks of the planned randomization date, the duration of the pre-randomization phase can be extended by up to 4 weeks to allow additional time for resolution of the infection.)

- Treatment Period (Randomization Phase): up to 78 weeks
- Follow-Up Period (Randomization Phase): 12 weeks (post last dose)

**Concomitant Drug/Therapy**

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit (see Appendix 2 for a detailed listing of these agents):

- Anticoagulants (eg, warfarin, digabatrin) are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization
- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization

Subjects taking AChEIs or memantine must meet the following criteria in order to be included in the primary analyses:

- On a stable dose for 12 weeks before the baseline cognitive assessments at Visit 2
- Remain on a stable dose while on study

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for the primary analyses.

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if, in the opinion of the investigator, this will not interfere with study procedures or subject safety, and are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks.

**Assessments**

**Efficacy Assessments**

Derived ADCOMS: The derived ADCOMS represents a new approach to the analysis of selected items (12 total) from 3 fully validated and well established clinical tools, the ADAS-cog (4 items), the MMSE (2 items), and the CDR (all 6 items). The 3 scales should be administered in full in the morning, or, if not possible, consistently at the same time of day.

Alzheimer's Disease Assessment Scale - cognitive subscale: The 14-item version will be used since it is considered more relevant for subjects with MCI/Prodromal AD or mild AD.

Mini Mental State Examination: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing.

Clinical Dementia Rating: Assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

CogState Brief Battery: A computer-based battery comprising 4 cognitive tests:

1. Detection – a simple reaction time test. Speed of response is the measure.
2. Identification – a simple choice reaction time test. Speed of response is the measure.
3. One Card Back – a simple working memory test. Accuracy of response is the measure.

4. One Card Learning – a visual learning and memory test. Accuracy of response is the measure.

International Shopping List Task: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall.

Functional Assessment Questionnaire: The FAQ has 10 items concerned with performing daily tasks necessary for independent living. Either a caregiver or informant or the subject provides performance ratings on 10 complex activities of daily living performed within the preceding 4 weeks.

Volumetric Magnetic Resonance Imaging: vMRI will be used to evaluate disease modification, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs.

**Pharmacokinetic Assessments**

Blood and CSF samples will be collected for the determination of the concentrations of E2609. Analyses of metabolite concentrations may be performed depending on emerging data from other studies with E2609.

**Pharmacodynamic, Pharmacogenomic and Other Biomarker Assessments**

Brain atrophy will be measured by vMRI: see Efficacy Assessments (above).

The soluble biomarkers Aβ(1-x), Aβ(1-42), total tau (t-tau), and p-tau will be measured in CSF. BACE1 levels and activity in CSF will also be measured. Other exploratory biomarkers (eg, miRNA) may also be evaluated in plasma and/or CSF.

Amyloid PET imaging will be used to confirm that all subjects eligible for progression to the Baseline Period of the study have amyloid deposition in the brain. Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted through to the time at which acceptable 18-month PET scans have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used.

Apolipoprotein E (*ApoE*) and *NAT2* genotyping/phenotyping will be conducted. *ApoE4* homozygous or heterozygous status versus non-carriers and *NAT2* status will be used in the statistical analysis to determine the effects on treatment response and safety. Remaining genomic DNA may also be stored for up to 15 years to be used to examine the role of DNA sequence variability on the absorption, distribution, metabolism, and elimination of E2609, development of AEs, as well as the underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single-nucleotide polymorphisms with PK, safety, or PD data.

**Safety Assessments**

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments. Routine safety assessments will include the monitoring and recording all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological

assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up. Subjects reporting AEs

relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

Complete blood counts and lymphocyte subset absolute counts and percentages will be measured (by a centralized laboratory) every week for the first month, every 2 weeks for the next 2 months (Months 2 and 3) and monthly for the next 3 months (Months 4, 5, and 6). Thereafter they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits. Serum IgG, IgA, and IgM will be monitored monthly for the first 3 months, at 6, 12, and 18 months, and at both Follow-Up Visits.

Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and posttreatment for exploratory immunomodulatory and immune-based analyses.

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at baseline and at 3-month intervals during the Treatment Phase of the study. These assessments will specifically include evaluation of any areas of depigmentation or rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregivers/ informants will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so such AEs can be reviewed promptly.

Baseline and on-study blood, DNA, and CSF samples will be taken and stored from all subjects. These samples may be tested for exploratory biomarkers associated with study drug or disease, or in the event that a subject develops AEs that warrant further investigation (eg, to test if a subject with a treatment-emergent infection was exposed to any suspected infective agents before treatment with study drug).

Safety brain MRI assessments will be performed at Screening, at 6, 12, and 18 months during the Treatment Phase of the study and at the final Follow-Up Visit. Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Full neurological examinations will be performed at Baseline, at 6, 12, and 18 months, and at both Follow-Up Visits, by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations. The neurological examinations will include muscle strength testing and assessment of cranial nerves including olfaction as well as other parts of the CNS.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments will include the ADAS-$cog_{14}$, MMSE, and CBB.

An assessment of suicidality using the C-SSRS will be performed at Screening and Baseline and at regular intervals throughout the treatment and Follow-Up periods of the study.

An ophthalmic examination (including retinal examination) will be conducted at Baseline. An additional examination will be conducted if the subject experiences visual disturbances during the course of the study.

A number of safety-related criteria for discontinuation of study drug are specified for the study.

**Bioanalytical Methods**

Plasma and CSF concentrations of E2609 will be measured by a validated liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) in both CSF and plasma will be measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and post-screening analysis of CSF Aβ(1-42), tau, and p-tau will be performed using ELISAs.

BACE1 levels and activity may be measured using a customized assay. Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

**Statistical Methods**

All statistical tests will be based on the 5% (2-sided) level of significance, except for the Bayesian methods on the primary endpoint.

**Study Endpoints**

**Primary Endpoint**

- Change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects

**Secondary Endpoints**

Change from baseline in:

- Total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- CSF Aβ(1-x) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
- The derived ADCOMS at 18 months of treatment in mild AD subjects

**Exploratory Endpoints**

Change from baseline in:

- The derived ADCOMS at 12 months of treatment in MCI/Prodromal and mild AD subjects
- Total hippocampal volume at 12 and 18 months of treatment in mild AD subjects as measured by vMRI
- CSF Aβ(1-42) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
- CSF Aβ(1-x) and Aβ(1-42) after 4 weeks and 18 months of treatment in mild AD subjects

- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ in MCI/Prodromal and mild AD subjects
- CSF biomarkers of neurodegeneration (eg, tau and p-tau) at 18 months of treatment in MCI/Prodromal and mild AD subjects
- Plasma and CSF amyloid, and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild AD subjects
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and, 18 months in MCI/Prodromal and mild AD subjects as measured by vMRI
- Brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild AD subjects
- The population PK parameters of E2609 including the effect of intrinsic and extrinsic factors (including *NAT2* phenotype) in MCI/Prodromal and mild AD subjects

**Analysis Sets**

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set is the subset of subjects in the FAS who sufficiently comply with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

**Efficacy Analyses**

***The MCI/Prodromal cohort:*** This study in the MCI/Prodromal cohort is based on Bayesian adaptive design. Frequent interim analyses will be performed to assess the probability of early success and futility and to make early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis. Key definitions relevant to the Bayesian aspects of the adaptive design are given below.

**Study Definitions**

- **Maximum Effective Dose ($d_{Max}$):** The dose that achieves the greatest treatment effect.
- **$ED_{90}$:** The lowest dose that achieves at least 90% of the $d_{Max}$ treatment effect in the derived ADCOMS.

- **Early Success:** The study in the MCI/Prodromal cohort will meet early success criteria if the probability that the $ED_{90}$ at 18 months of treatment achieves 25% improvement over placebo is at least 80%. Early success is achieved before all MCI/Prodromal subjects complete 18 months of treatment and can only be determined after at least 200 MCI/Prodromal subjects have been randomized. If early success is declared before full randomization, the randomization of new MCI/Prodromal subjects will stop but subjects already randomized into the study will receive the full 18 months of treatment (following confirmation from the Sponsor's Senior Management).
- **Futility:** The study in the MCI/Prodromal cohort will meet statistical futility criteria if the probability that the $ED_{90}$ is better than placebo by the clinically significant difference of 25% is less than 5% at 18 months of treatment. The statistical futility boundary is binding; if the statistical futility boundary is crossed the study will be considered to have failed.
- **Study Success:** The study in the MCI/Prodromal cohort will be considered a success if an $ED_{90}$ at 18 months treatment has at least an 80% probability of achieving 25% improvement over placebo at either an interim analysis or at the final analysis.

***The Mild AD cohort:*** The analysis of the Mild AD cohort is based on the group sequential design. Interim analyses in the Mild AD cohort will only be performed after the MCI/Prodromal cohort crosses the early success boundary. The early efficacy signal based on the change from baseline of ADCOMS at 18 months is defined as crossing the interim-analysis boundaries for overwhelming efficacy in the mild AD population. The O'Brien-Fleming (OF) boundaries based on Lan-DeMets alpha spending function will be used to assess overwhelming efficacy. The corresponding OF boundaries based on *P* values will be 0.076, 0.0221, and 0.0423 for the first, second, and final analyses, respectively, according to 2 planned interim analyses at the 60% and 80% information fraction.

**Analysis for the primary endpoint**

***Primary analysis of primary endpoint***

The primary analysis will be based on MCI/Prodromal subjects from the FAS with the prespecified censoring rule applied. The primary endpoint is the change from baseline to 18 months in the derived ADCOMS. The dose-response of the primary endpoint is modelled with a first-order normal dynamic linear model, where Normal and Inverse-Gamma priors are used. The primary efficacy analysis will calculate the Bayesian posterior probability that the dose identified is the most likely $ED_{90}$ dose that achieves 25% improvement over the placebo arm. At each interim analysis and the final analysis, 2 Bayesian probabilities will be summarized for each active dose: the probability it is the $ED_{90}$ dose and the probability of achieving 25% improvement over the placebo arm.

For the clinical efficacy data (ie, derived ADCOMS, MMSE, ADAS-cog, etc), subjects will be censored at the time of initiation of treatment with AChEIs or memantine, if they were not on these medications at the time of Baseline cognitive assessment (Visit 2), and will be censored at the time of dose adjustment of AChEIs or memantine if they were already on stable treatment with these medications at the time of Baseline cognitive assessment

(Visit 2). The value of the primary endpoint for censored subjects will be imputed using data up to the censoring time and Bayesian longitudinal modeling.

***Sensitivity analyses of primary endpoint***

After unblinding, the primary endpoint will be analyzed using the Bayesian methods described above as well as conventional statistical methods. The following additional Bayesian analyses will be conducted as sensitivity analyses:

- The primary endpoint will be analyzed regardless of initiation of treatment, or dose adjustment, with AChEIs or memantine using the same Bayesian analysis method as primary analysis. This is an intent-to-treat analysis without any censoring.
- In case of early success, the primary analysis as well as the above sensitivity analyses will be repeated after all subjects have completed 18 months of treatment or have been lost to follow-up.

Statistical methods for the final conventional analyses will use a mixed-effects model with repeated measures (MMRM) on the change from baseline in the derived ADCOMS at 18 months. The model will include treatment groups, randomization stratification variables (the presence or absence of ongoing treatment with AChEIs or memantine or both, and *ApoE4* status), and baseline ADCOMS as covariates. Other covariates such as adjusted hippocampal volume will be studied. These analyses will be performed as sensitivity analyses on the FAS as well as the per protocol set, and as such, no multiplicity adjustments will be made to account for the interim analyses. In case of early success, the conventional analyses will also be performed using the data collected before the interim analysis.

**Analysis for the secondary endpoints**

***The MCI/Prodromal cohort***

An MMRM will be used to analyze the following secondary endpoints:

- Change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-x) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects. Data from early discontinuations will also be included.

Comparisons between each treatment group and placebo will be performed.

***The Mild AD cohort***

An MMRM will be used to analyze the change from baseline of derived ADCOMS at 18 months in mild AD. If there is no treatment group-by-population interaction in the overall study, the MMRM analysis will include all subjects (MCI/Prodromal or mild AD) in the overall study. Otherwise, the MMRM analysis will only include subjects in the mild AD cohort. The comparison between placebo and active doses will be performed within mild AD subjects regardless of subjects included in the MMRM analysis. Dunnett's method will be used to control for multiplicity due to multiple comparisons.

**Analysis for exploratory endpoints**

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in the derived ADCOMS at 12 months in MCI/Prodromal and mild AD subjects
- Change from baseline in total hippocampal atrophy at 12 and 18 months in mild AD subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-42) after 4 weeks and 18 months in MCI/Prodromal subjects. Data from early discontinuations will also be included.
- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) after 4 weeks and 18 months in mild AD subjects. Data from early discontinuations will also be included.
- Change from baseline in the clinical assessments: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months in MCI/Prodromal and mild AD subjects
- Change from baseline in plasma and CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild AD subjects
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and 18 months as measured by vMRI in MCI/Prodromal and mild AD subjects

A linear mixed-model will be used to analyze the following exploratory endpoints:

- Change from baseline in brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild AD subjects
- Change from baseline in CSF biomarkers of neurodegeneration (eg, tau, p-tau) at 18 months of treatment in MCI/Prodromal and mild AD subjects

Data from early discontinuations will also be used as appropriate. Comparisons between each treatment group and placebo will be performed.

A linear mixed-model with repeated measures will be used to determine the relationship between the following endpoints:

- Change from baseline in the derived ADCOMS score and the change from baseline in biomarkers in CSF at 18 months in MCI/Prodromal and mild AD subjects
- Change from baseline in the derived ADCOMS score and change from baseline in imaging biomarkers (hippocampal, whole brain, and total ventricular volumes) at 12 and 18 months in MCI/Prodromal and mild AD subjects

*ApoE* status for heterozygous and homozygous E4 carriers will be included in the model to assess the effect of *ApoE* status in this relationship.

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). CSF Aβ(1-x), Aβ(1-42), t-tau, p-tau, and BACE1 will be assessed and data will be presented graphically. Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status. Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels and exposure to E2609 in plasma and CSF will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. Additionally, the relationship between CSF exposure to E2609 and the derived ADCOMS at 18 months, and the relationship between CSF exposure to E2609 and the change from baseline for 18 months in the ADAS-cog, the CDR, and the

MMSE will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling.

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. Further information is in the "Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments" section. Details of pharmacogenomic testing may be provided and reported separately.

**Safety Analyses**

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, and vital sign measurements will be summarized by treatment group using descriptive statistics.

Lymphocyte Subsets

Lymphocyte subsets (ie, CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages]) and regulatory T cells will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose. Serum IgG, IgM, IgA will be measured and summarized in the same manner as other laboratory parameters.

**Interim Analyses**

***The MCI/Prodromal cohort***

Oversight of the Bayesian interim analyses and response adaptive randomization will be conducted by an independent committee that has expertise with Bayesian adaptive design in clinical studies. An unblinded external independent analysis group will provide the interim analysis outcomes to the committee at each interim analysis. The committee will ensure the integrity of the interim analysis and response adaptive randomization process through review of efficacy data. In addition, the committee will act in an independent advisory capacity to monitor the Bayesian interim analysis outcomes according to the early success and futility boundaries prespecified in the protocol. The committee will not be charged with any subject safety issues; this will remain the responsibility of the DSMB. The DSMB will continue to

monitor the safety aspects of the study throughout Stage A and Stage B. The study may be stopped for safety at any time.

An interim safety analysis will be conducted when the first 60 MCI/Prodromal subjects have completed 12 weeks of treatment (or discontinue study drug early). The first Bayesian adaptive interim analysis will be conducted when 100 MCI/Prodromal subjects have been randomized into the study (ie, 60 subjects from Stage A and the first 40 subjects from Stage B of the study). Further interim efficacy analyses will be conducted after each additional 50 MCI/Prodromal subjects have been randomized, up to a maximum of 500 MCI/Prodromal subjects (ie, at 100, 150, 200, 250, 300, 350, 400, 450, 500 subjects randomized). If the study reaches full randomization, additional interim analyses will be conducted every 3 months until all subjects complete 18 months of treatment. The study will be monitored for futility at each interim analysis. Starting at the 200 subjects' interim analysis, the study will be monitored for success at each interim analysis. Each interim analysis will be conducted on data for the derived ADCOMS.

If the predefined early success criteria are met during the recruitment period, further recruitment and enrollment of MCI/Prodromal subjects into the study will stop (following confirmation from the Sponsor's Senior Management) and all currently randomized subjects will complete the full 18 months of treatment. No further interim analyses will be conducted after achieving early success.

If the predefined threshold for futility is reached, no additional subjects will be randomized into the study and the treatment of subjects already randomized into the study will stop and the study will be declared as "failed". All subjects will be monitored for safety for 3 months following their last dose.

If neither early success nor futility is reached and the study reaches full randomization, all subjects will complete 18 months of treatment. Interim efficacy analyses will be conducted every 3 months after full randomization is reached to assess futility and early success until all subjects complete 18 months of treatment. After full randomization, all study subjects will stop treatment only in the event of futility.

***The Mild AD cohort***

A group sequential design will be used for the mild AD cohort. This design includes 3 looks, 2 interim looks (when 60% and 80% information fractions are achieved) and 1 final look. Interim analyses will be performed after the MCI/Prodromal cohort crosses the early success boundary. The corresponding efficacy boundaries will be 0.076, 0.022, and 0.0423 for the first, second, and final analyses, respectively. If the actual information fraction during the interim analyses is different from 60% or 80% at the interim, the efficacy boundaries will be adjusted based on the actual information fraction. If early success in the MCI/Prodromal cohort is not achieved before the final analysis that is performed when all subjects have completed 18 months treatment, then only a final analysis will be performed in mild AD subjects. In the event of futility in the MCI/Prodromal cohort, an analysis will be performed for the mild AD cohort based on the data for mild AD subjects available at that time.

**Adaptive randomization in the MCI/Prodromal cohort**

Randomization to placebo or 1 of 3 dose groups of E2609 will be fixed for the first 100 subjects randomized in the study (1:1:1:1; placebo to each of the 3 active doses [60 patients in Stage A and the first 40 patients in Stage B]). Randomization probabilities to each treatment group will be updated at each interim analysis, such that the randomization probability will be increased for the placebo group and dosage groups that represent the potential target dose ($ED_{90}$), and simultaneously decreased for other active arms. Randomization in the Mild AD cohort will remain at a fixed schedule throughout Stage B.

Within the 2 clinical populations (MCI/Prodromal and mild AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no).

**Sample Size Rationale**

***Sample Size Rationale in the MCI/Prodromal cohort***

Primary endpoint – derived ADCOMS: The sample size and design characteristics to test the hypothesis for the primary objective based on the primary endpoint were determined by means of simulations. Extensive study simulations have shown that a total of 500 subjects will be sufficient to demonstrate that the most likely $ED_{90}$ dose achieves a 25% improvement over placebo with a probability of at least 80% in the interim and final analyses. There is at least a 90% probability of study success for the dose response scenarios where treatment was considered to have a clinically meaningful treatment effect. Simulations have also shown that if there is no obvious dose effect, the probability of falsely claiming superiority to placebo is at most 5%.

For each of the 4 treatment groups (3 active doses and placebo), the final number of subjects per group will differ depending on the observed interim treatment responses.

vMRI: The null hypothesis is that there is no difference between active dose and placebo. There are 3 null hypotheses corresponding to 3 active doses. The alternative hypothesis is that at least 1 null hypothesis is false (1-sided). The null hypotheses will be tested using Dunnett's method with 1-sided alpha of 0.05. The statistical power was estimated through simulation for a moderate dose-response assumption that the percent reduction in change from baseline of total hippocampal volume compared with placebo would be 15%, 20%, and 25% corresponding to the 3 doses, respectively. The estimated power for actual planned study sample size is 78% at 18 months assuming an attrition rate of 20% at 18 months. Under a stronger dose-response assumption (ie, the percent reduction in change from baseline of total hippocampal volume compared with placebo is twice as much as that in the moderate dose-response assumption), the estimated power is at least 99% at 18 months.

Amyloid PET: The null and alternative hypotheses and statistical test are the same as those for vMRI. To estimate the sample size for the amyloid PET imaging subgroup at 18 months, a common SD of change from baseline was estimated at 0.33 and a reasonable mean difference between treatment and placebo was estimated as 0.25 (standardized uptake value ratio [SUVR]). Assuming a moderate dose-response, the best dose would achieve a difference of 0.25 (SUVR) and the middle and low doses would achieve a difference of 0.2

and 0.15 (SUVR), respectively, it would require a total of 100 subjects from all 4 arms at 18 months to achieve 80% power.

***Sample Size Rationale for the Mild AD Cohort***

ADCOMS at Month 18: The null hypothesis is that there is no difference between active dose and placebo. There are 2 null hypotheses corresponding to 2 active doses. The alternative hypothesis is that at least 1 null hypothesis is false. The null hypotheses will be tested using Dunnett's test with 2-sided alpha of 0.05 as described for the mild AD cohort in the secondary analysis section. The statistical power was estimated through simulation for the dose-response assumption that the percent reduction in change from baseline of ADCOMS at 18 months compared with placebo would be 33% and 50% corresponding to the 2 doses, respectively. The estimated power for the actual planned 200 mild AD subjects is at least 80% assuming a 2-sided alpha of 0.05.

# 3 TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES



## LIST OF IN-TEXT FIGURES



## LIST OF APPENDICES

# 4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| Aβ | amyloid β |
| Aβ(1-x) | amyloid β (1-x) (ie, the amyloid β monomer from amino acid 1 to x [eg 1-42]) |
| AChEI | Acetylcholinesterase inhibitor |
| AD | Alzheimer's disease |
| ADAS-cog | Alzheimer's Disease Assessment Scale - cognitive subscale |
| ADCOMS | Alzheimer's Disease Composite Score |
| AE | Adverse Event |
| ApoE | Apolipoprotein E |
| AUC | area under the concentration x time curve |
| $AUC_{(0\text{-}24h)ss}$ | area under the concentration x time curve at steady state from time zero to 24 hours |
| BACE1 | Beta-amyloid converting enzyme 1 |
| BP | blood pressure |
| bpm | beats per minute |
| CBB | CogState Brief Battery |
| CBP | childbearing potential |
| CDR | Clinical Dementia Rating |
| CES2 | carobxyesterase-2 |
| CFR | Code of Federal Regulations |
| $C_{max,ss}$ | maximum plasma concentration at steady state |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| CRA | clinical research associate |
| CRF | case report form |
| CRO | contract research organization |
| CSF | cerebrospinal fluid |
| $C_{ss,av}$ | average steady-state concentration |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CTA | Clinical Trial Agreement |
| CYP | cytochrome P450 |
| $d_{Max}$ | Maximum effective dose |
| DSMB | data safety monitoring board |
| ECG | electrocardiogram |
| eCRF | electronic case report form |

| Abbreviation | Term |
|---|---|
| ED | early discontinuation |
| $ED_{90}$ | lowest effective dose that achieves 90% of the greatest treatment effect |
| ELISA | enzyme-linked immunosorbent assay |
| FAQ | Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire) |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FLAIR | fluid-attenuated inversion recovery |
| GCP | Good Clinical Practice |
| GDS | Geriatric Depression Scale |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |
| HCVAb | hepatitis C virus antibody |
| HSV | herpes simplex virus |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ID | identifier |
| IEC | Independent Ethics Committee |
| Ig | immunoglobulin (eg, IgA, IgG, IgM) |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISLT | International Shopping List Task |
| IxRS | interactive voice and web response system |
| LLN | lower limit of normal |
| LNH | low/normal/high |
| LP | lumbar puncture |
| MAD | multiple ascending dose |
| MCI | mild cognitive impairment |
| MCI/Prodromal | Mild Cognitive Impairment due to Alzheimer's Disease/ Prodromal Alzheimer's Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mild AD | mild dementia due to Alzheimer's Disease |
| miRNA | micro-ribonucleic acid |
| MMRM | mixed-effects model with repeated measures |
| MMSE | Mini Mental State Examination |
| MRI | magnetic resonance imaging |

| Abbreviation | Term |
|---|---|
| NAT2 | N-acetyltransferase 2 |
| NIA-AA | National Institute on Aging-Alzheimer's Association |
| OF | O'Brien-Fleming |
| PBMC | peripheral blood mononuclear cell |
| PD | Pharmacodynamic(s) |
| PET | positron emission tomography |
| PGx | pharmacogenomic(s) |
| PK | pharmacokinetic(s) |
| PP | per protocol |
| PRN | Pro re nata |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| p-tau | phosphorylated-tau |
| QD | once daily |
| QTc | corrected QT interval |
| QTcF | QTc interval calculated using Fridericia's formula |
| R | randomization |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reaction |
| SUVR | standardized uptake value ratio |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |
| TEMAV | treatment-emergent markedly abnormal laboratory values |
| t-tau | total tau |
| ULN | upper limit of normal |
| UNS | unscheduled |
| vMRI | volumetric magnetic resonance imaging |
| WHO DD | World Health Organization Drug Dictionary |
| β-hCG | beta-human chorionic gonadotropin |

Study References: On first use, the full study code will be used (eg, E2609-G000-202) with a shortened form in brackets (Study 202); thereafter, the shortened form is used.

# 5 ETHICS

## 5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA][s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigators or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

## 5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (CFR) (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

- European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved European Union member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

## 5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject and the identified caregiver or informant, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if the identified caregiver or informant is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject and the identified caregiver or informant, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified caregiver or informant should also consent to supporting the subject's participation in the study and will be provided with a separate written ICF for his or her participation in the study, to be signed before he or she participates in any further aspects of the study.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified caregiver or informant must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified caregiver or informant will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified caregiver or informant should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

# 6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 125 investigational sites globally (25 sites in the United States for Stage A and 125 sites globally for Stage B).

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

# 7 INTRODUCTION

At this time, there is no cure for Alzheimer's disease (AD), no known way of slowing down the progression of this disease, and no approved treatment available to reverse the deterioration. There is, therefore, an urgent unmet medical need for drugs that slow or prevent disease progression. Beta-amyloid converting enzyme 1 (BACE1) is a key enzyme responsible for the production of amyloid β (Aβ) peptides and plaque formation, and several reports have described elevated levels of BACE1 in AD brains (Coulson, et al., 2010, Lu, et al., 2012). Once amyloid plaques form, Aβ causes BACE1 levels to increase further, thus accelerating Aβ generation and plaque growth via a positive feedback loop. Therefore, BACE1 is a promising target for modifying or treating AD.

It is now widely accepted that mild cognitive impairment (MCI) due to AD and mild AD dementia are stages on a single disease spectrum, which follows an Alzheimer's pathological cascade. Recent consensus papers from the international workgroups of the National Institute on Aging-Alzheimer's Association (NIA-AA), have endorsed this hypothesis (Albert, et al., 2011; Jack, et al., 2011; McKhann, et al., 2011; Sperling, et al., 2011).

From a clinical standpoint, demonstration of an effect on slowing disease course is hampered by the lack of sensitive tools for detecting relatively small changes in progression or treatment effect especially in early disease. In addition, drugs that are expected to slow disease progression require longer study durations to ensure adequate separation from placebo. These challenges have resulted in the use of biomarkers as surrogates for clinical effect in Phase 2 studies, in order to facilitate the development process for disease modifying agents. However, subsequent Phase 3 AD studies based solely on biomarker findings in Phase 2 have failed to show clinical effect, due, in part, to the fact that biomarkers may not predict clinical outcomes for potential disease modifying agents. These findings underscore the need for innovative approaches to clinical study design for measuring the effect of treatment.

E2609 is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, E2609 inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in cerebrospinal fluid (CSF) and plasma (rat, guinea pig, and monkey). In humans, E2609 has been shown to inhibit BACE1 enzyme activity in CSF and lower the levels of Aβ, including amyloid beta monomer from amino acid 1 to x (Aβ[1-x]), Aβ(1-40) and Aβ(1-42), in CSF both in vitro and in vivo. See the Investigator's Brochure for additional information. The target indication for E2609 is therefore treatment and disease modification of AD.

The present clinical study represents the sole Phase 2 study for the E2609 program, and is designed to establish Proof of Concept in subjects with Mild Cognitive Impairment due to Alzheimer's Disease/Prodromal Alzheimer's Disease (referred to as MCI/Prodromal throughout the protocol). The study also allows investigation of efficacy in subjects with mild dementia due to Alzheimer's Disease (referred to as mild AD throughout the protocol) to determine whether the effects of E2609 in this later stage population are comparable with those established in the MCI/Prodromal population within this same study. In the MCI/Prodromal population, Bayesian response adaptive randomization design is used with

frequent interim analyses to continually update randomization allocation based on emerging clinical endpoint data. This approach allows for ongoing assessment of drug futility or evidence of early success and can mitigate the risks associated with larger and longer studies required to demonstrate clinical efficacy by leading to more efficient study termination or early advancement to a Phase 3 program. Results from this study will guide both the decision to move into Phase 3 development and the selection of the dose strengths to be taken into Phase 3. Moreover, this study is intended to be supportive for registration in the MCI/Prodromal population.

In the MCI/Prodromal population, this study will compare placebo and 3 oral doses of E2609 (5 mg, 15 mg and 50 mg) administered once daily (QD) for 18 months. In the mild AD population, this study will compare placebo and 2 oral doses of E2609 (15 mg and 50 mg) administered QD for 18 months. To date, the longest duration of dosing with E2609 is 14 days (multiple ascending dose [MAD] Study E2609-A001-002 [Study 002]).

This study (E2609-G000-202 [Study 202]) will comprise 2 stages: Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 in the United States sites only, before expanding enrollment to a larger and more global population of subjects in Stage B. This design will allow close monitoring of safety by an independent data safety monitoring board (DSMB), including a formal safety review as soon as the first 60 randomized subjects have completed 12 weeks of treatment, have discontinued study drug or have withdrawn from the study. The study also includes a number of exclusion criteria, specific blinded safety monitoring procedures and safety criteria for discontinuation of study drug in light of the preclinical and clinical safety data collected to date following administration of E2609.

## 7.1 Nonclinical and Clinical Safety Data

The toxicity of E2609 has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomologus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by E2609 in a clinical setting. Further details of the nonclinical data to date with E2609 can be found in the Investigator's Brochure.

The clinical program to date includes 6 Phase 1 studies:

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, single ascending dose (SAD) study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled MAD study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the

14 days of dosing so as to assess the pharmacokinetic (PK) levels of E2609 and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of E2609. It also investigated the effects of E2609 on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [$^{14}$C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of E2609 under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) was a randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with E2609. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with E2609. In elderly subjects treated with 50 mg of E2609, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTc interval calculated using Fridericia's formula (QTcF) from baseline (14.9 msec at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of E2609 might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that E2609 altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of E2609. A single dose of E2609 up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, E2609 administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment

by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of E2609 on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP3A4] and carboxyesterase-2 [CES2]) increased by approximately 70% the area under the concentration × time curve (AUC) of E2609. Consequently, strong inhibitors of CY3A4 will be prohibited in this study.

Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of E2609. Therefore, no restrictions are required for the use of concomitant medications which are known to be inducers of CYP450 enzymes. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of E2609 when coadministered with E2609 but not when dosed at least 2 hours apart from E2609. E2609 (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of E2609. Therefore, on the basis of drug interaction considerations, the only restriction of concomitant medications is that for strong inhibitors of CYP3A4.

# 8 STUDY OBJECTIVES

## 8.1 Primary Objectives

The primary objectives are:

1. To evaluate the efficacy of daily dosing with 3 doses of E2609 compared with placebo by establishing the lowest effective dose that achieves 90% of the greatest treatment effect ($ED_{90}$) for E2609 on the derived Alzheimer's Disease Composite Score (ADCOMS) at 18 months of treatment in subjects with MCI/Prodromal
2. To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with mild AD

## 8.2 Secondary Objectives

The secondary objectives are:

1. To evaluate the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects, as measured by volumetric magnetic resonance imaging (vMRI)
2. To evaluate the effect of E2609 compared with placebo on Aβ(1-x) in CSF after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
3. To evaluate the efficacy of E2609 compared with placebo on the derived ADCOMS at 18 months in mild AD subjects

## 8.3 Exploratory Objectives

The exploratory objectives are:

1. To explore the effect of E2609 compared with placebo on the derived ADCOMS following 12 months of treatment in MCI/Prodromal and mild AD subjects
2. To explore the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in mild AD subjects, as measured by vMRI
3. To explore the effects of E2609 compared with placebo on Aβ(1-42) in CSF after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
4. To explore the effects of E2609 compared with placebo on Aβ(1-x) and Aβ (1-42) in CSF after 4 weeks and 18 months of treatment in mild AD subjects

5. To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during posttreatment follow-up, in MCI/Prodromal and mild AD subjects, by assessment of:
   a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
   b. The Clinical Dementia Rating (CDR) scale
   c. The Mini-Mental State Examination (MMSE)
   d. The CogState Brief Battery (CBB)
   e. The Functional Assessment Questionnaire (FAQ; (also known as the Functional Activities Questionnaire)
   f. The International Shopping List Task (ISLT)
6. To explore the effects of E2609 compared with placebo on various biomarkers in MCI/Prodromal and mild AD subjects. Biomarkers to be explored include:
   a. CSF biomarkers of neurodegeneration (eg, tau, phosphorylated-tau [p-tau]) after 18 months of treatment
   b. Plasma and CSF amyloid, and CSF BACE1 measurements during 18 months of treatment and during posttreatment follow-up
   c. vMRI measurements including left and right hippocampal volume, whole brain volume, and total ventricular volume at 6, 12, and 18 months of treatment and during posttreatment follow-up
   d. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)
7. To characterize the population PK of E2609 in MCI/Prodromal and mild AD subjects, and to examine the effect of intrinsic and extrinsic factors (including N-acetyltransferase 2 [*NAT2*] phenotype) on the PK
8. To explore the relationship between the treatment effects of E2609 on the ADCOMS and its effects on CSF amyloid, CSF BACE1, CSF tau, and vMRI in MCI/Prodromal and mild AD subjects

# 9 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan

Study 202 is a multicenter placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild AD.

A common set of inclusion criteria, consistent with the NIA-AA clinical research criteria for MCI due to AD or mild AD, will be required for all subjects. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). As the non-demented subjects will be consistent with criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria.

The study will be conducted in 2 stages, Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 (at least 12 weeks) in MCI/Prodromal subjects, before expanding enrollment to include a larger population of MCI/Prodromal subjects in Stage B (maximum of approximately 500 subjects across both stages). In addition, during Stage B of the study, subjects with mild AD will be recruited into a separate cohort (approximately 200 subjects). All MCI/Prodromal subjects will be included in the primary efficacy evaluation irrespective of whether they were recruited into Stage A or Stage B of the study.

Both Stage A and Stage B of the study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days) will consist of a Screening Visit and a Baseline Visit. Screening assessments will be organized into 4 tiers; see Section 9.5.2.2, Table 6, and Figure 2.

All screening assessments must be completed, and eligibility to continue to the Baseline Period confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

MCI/Prodromal subjects will be randomized to 4 treatment groups (E2609 at 3 doses or placebo, with an initial ratio of 1:1:1:1) and this recruitment will take place during both Stage A and Stage B. Bayesian adaptive randomization will be used in Stage B in the MCI/Prodromal cohort. Subjects with mild AD who are recruited in Stage B will be randomized to 3 treatment groups (E2609 at 2 doses or placebo).

An overview of the study design is presented in Figure 1.

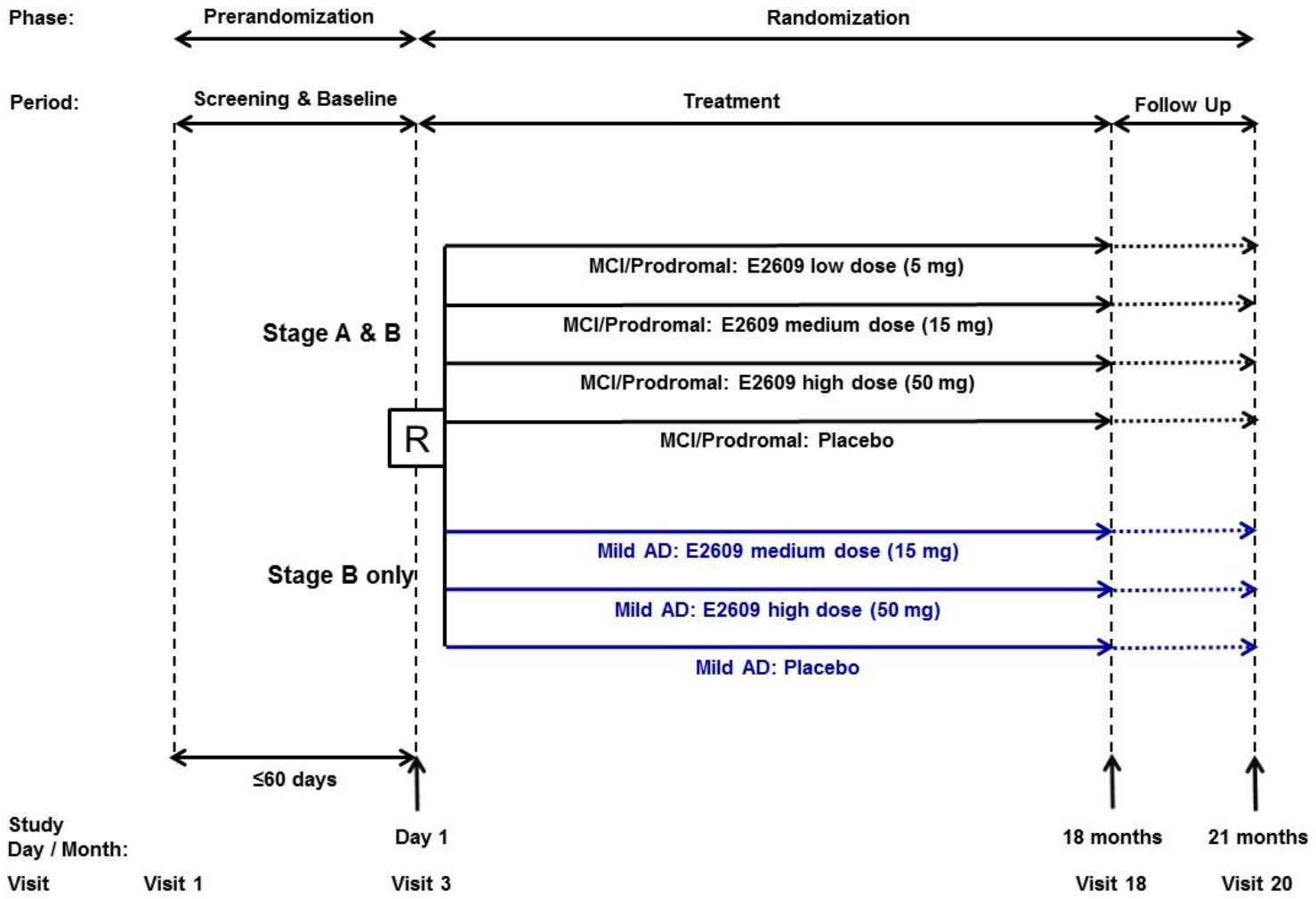



**Figure 1 Design of Study E2609-G000-202**

R = randomization.

**Stage A**

Stage A of the study will be limited to approximately 25 clinical centers in the United States. Stage A will randomize 60 eligible MCI/Prodromal AD subjects 1:1:1:1 to 4 treatment groups. There will be no Bayesian adaptation during Stage A of the study. In addition to the placebo group, 3 doses of E2609 will be used to reduce CSF Aβ levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/PD modeling shows these doses should achieve these targets when administered QD with food and will be confirmed or adjusted based on the 4-week assessment of CSF Aβ(1-x) (see Section 9.4.4).

During Stage A, safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the first subject is randomized during Stage A of the study, an independent DSMB (including at least 1 immunologist) will review all safety data in an unblinded manner. The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. Unless the DSMB recommends otherwise, randomization of subjects into Stage A of the study will continue until 60 MCI/Prodromal subjects have been randomized and dosed.

After 60 MCI/Prodromal subjects in Stage A have completed 4 weeks of treatment, an interim analysis of the E2609 PK and PD profiles will be used to confirm the E2609 doses to be used for Stage B of the study (see Section 9.4.4).

Once 60 MCI/Prodromal subjects in Stage A have completed at least 12 weeks of treatment (or discontinued study drug early) an interim safety analysis will be conducted by Eisai and the DSMB. Subjects in Stage A will continue study drug while the DSMB reviews all the available safety data, but randomization of additional subjects will not take place (ie, recruitment into Stage B will not commence) until the safety analysis is completed by the DSMB. At the time of this interim safety analysis, some subjects will have more than 12 weeks of safety data.

If there are safety signals with one of the E2609 dose groups that would require dose adjustment, changes to dose will be reflected in an amendment to the protocol. Information on how these subjects will be handled in the primary analysis will be described in the Statistical Analysis Plan.

**Stage B**

Stage B of the study will start after the DSMB safety review of Stage A has shown acceptable safety and tolerability of E2609 and after the doses of E2609 to be used in Stage B are confirmed. Based on data from Stage A, the protocol will be reviewed and may be amended before beginning Stage B. Safety data from Stage B will continue to be reviewed by the DSMB (approximately every 3 months) until recruitment in the study is completed; following this the DSMB will meet approximately every 6 months.

Stage B of the study will be conducted globally and will enroll, randomize, and dose up to an additional 440 eligible MCI/Prodromal subjects; the final total number will depend upon

whether the prespecified criteria for either early success or futility are met. In addition, a separate cohort of approximately 200 mild AD subjects will be randomized and dosed during Stage B.

Both population cohorts will include separate placebo groups. The MCI/Prodromal cohort will include 3 doses of E2609 (5 mg, 15 mg, and 50 mg QD), whereas the mild AD cohort will only include 2 doses of E2609 (15 mg and 50 mg QD).

Bayesian adaptive randomization will be used in the MCI/Prodromal cohort during Stage B of the study. The first 40 MCI/Prodromal subjects recruited into Stage B will be randomized according to a fixed schedule (1:1:1:1; placebo:5 mg E2609:15 mg E2609:50 mg E2609) and the remaining subjects in the MCI/Prodromal cohort will be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. The mild AD subjects will be randomized according to a fixed schedule (1:1:1 placebo; 15 mg E2609; 50 mg E2609) throughout Stage B of the study.

Interim efficacy analyses are planned and are discussed in Section 9.7.3.

### 9.1.1 Prerandomization Phase

The Prerandomization Phase includes a Screening Visit and a Baseline Visit. All Screening Visit assessments must be completed and eligibility to progress must be confirmed before any Baseline Visit assessments are performed. All Screening Visit and Baseline Visit assessments must be completed within 50 days and a window of 7 to 10 days is to be observed between the completion of all Baseline Visit assessments and randomization into the study at Visit 3. Thus, the Prerandomization Phase will last for up to 60 days. The series of assessments conducted during this phase will determine eligibility for randomization into the study.

Inclusion criteria are discussed in Section 9.1 and detailed in Section 9.3.1. Before randomization the clinician will provide a judgment on the classification of a subject as either MCI/Prodromal (eligible for Stage A and Stage B) or likely mild AD (eligible for Stage B only). This judgment may be discussed and reviewed with the Sponsor or Sponsor's representative, as necessary.

#### 9.1.1.1 Screening Period

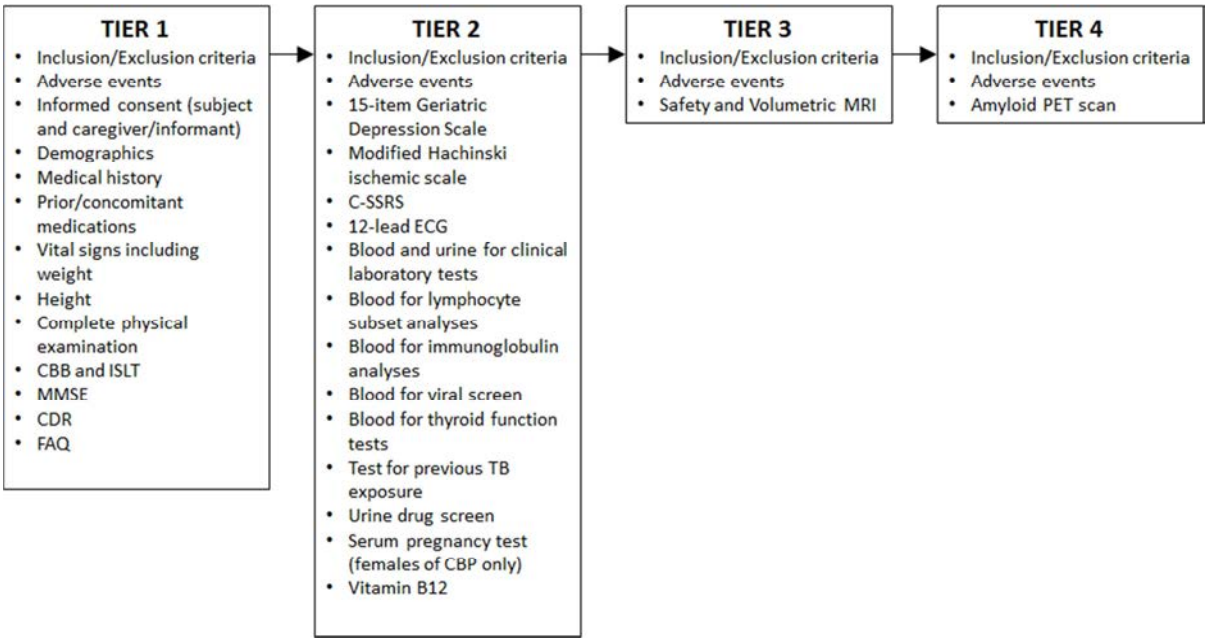
The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and caregiver or informant, and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained from both the subject and the caregiver or informant. The caregiver or informant needs to be present at this visit.

Study site personnel will interview the subject and caregiver or informant to obtain demographic and clinical information as described in Table 6, and will review inclusion and

exclusion criteria as described in Sections 9.3.1 and 9.3.2 and perform any required assessments in order to complete these criteria. Prior medications and medications currently being taken by the subject will be reviewed (see Section 9.4.7). The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

Clinical assessments for eligibility will be conducted during the Screening Visit as described in Table 6 and Figure 2.

Every effort should be made to conduct these assessments in the morning, but if this is not possible, they should be conducted at the same time of day at all subsequent visits. The screening assessments/procedures have been organized into 4 distinct tiers (Table 6 and Figure 2). All assessments/procedures in each tier should be completed, and eligibility to continue screening in the study confirmed, before any assessments/procedures from the next tier commence.




## Figure 2 Assessments to be Performed at Screening by Tier

CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), ISLT = International Shopping List Task (immediate and delayed recall), MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PET = positron emission tomography, TB = tuberculosis.

Cognitive assessments (Tier 1) are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). The order of assessments is: MMSE, CDR, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall) at Screening. The investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session (Tier 3).

Amyloid PET imaging will be used to confirm all subjects have amyloid deposition in the brain (Tier 4).

#### 9.1.1.2 Baseline Period

All Screening Visit assessments must be completed (and eligibility to progress confirmed) before any Baseline Visit assessments are performed. The Baseline Visit assessments (per Table 6 and Section 9.5.1.2) are to be completed as soon as possible after completion of the final Screening Visit assessment (ie, PET scan) such that all Screening Visit and Baseline Visit assessments are completed within 50 days.

Inclusion and exclusion criteria will again be reviewed, vital signs including weight will be recorded, and a 12-lead ECG will be conducted in triplicate. A routine physical examination will be conducted and a dermatological assessment and neurological examination will be performed. A urine pregnancy test will be conducted for females of childbearing potential. Blood will be collected from all subjects for clinical chemistry and hematology, lymphocyte subset analyses, Ig analyses, and PD assessments. Blood samples will be collected and stored for determination of a subject's previous exposure to infective pathogens in the event of AEs that warrant further investigation occurring at a later point in the study. Psychometric assessments will be administered to the subject in the order stated in Table 6. The caregiver or informant needs to be present at this visit. The Columbia Suicide Severity Rating Scale (C-SSRS) will also be administered (Section 9.5.1.5.11).

CSF will be obtained at this visit for PK and PD assessments (see Section 9.5.1.5.3).

Blood will be collected from all subjects for pharmacogenomic (PGx) analyses of apolipoprotein E (*ApoE*) and the *NAT2* phenotype of subjects enrolled in the study (see Section 9.7.1.7.2).

### 9.1.2 Randomization Phase

Subjects who complete the Baseline Visit assessments, and are eligible based on the inclusion and exclusion criteria (see Section 9.3.1 and Section 9.3.2), will begin the Randomization Phase within 7 to 10 days following completion of the Baseline Visit assessments.

The Randomization Phase will consist of a Treatment Period of 78 weeks duration and a Follow-Up Period of 12 weeks after the last dose of study drug.

#### 9.1.2.1 Treatment Period

Subjects will be randomized at the beginning of the Treatment Period and will receive study drug or placebo, to be administered orally QD with food. Double-blinding to study drugs will be in effect throughout the Treatment Period. The dose for a subject will not be changed during the study. However, dose adjustment for Stage B may be considered and subjects already randomized to a dose that needs to be adjusted will be switched to continue their treatment at the new adjusted dose.

Safety criteria for discontinuation of study drug are detailed in Section 9.3.3.

Subjects will attend the study site every week for the first 4 weeks after beginning study drug, then fortnightly until 12 weeks have elapsed since first dose. Visits will then be conducted at 16, 20, 26, 39, 52, 65, and 78 weeks after the first dose.

#### 9.1.2.2 Early Discontinuation

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug.

Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie. at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB and ISLT) will be conducted. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) after the Early Discontinuation Visit or within ± 8 days of either of the Follow-Up Visits (Visit 19 and Visit 20). Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

#### 9.1.2.3 Follow-up Period

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug (Visit 19) and a second 12 weeks after the last dose of study drug (Visit 20). If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the posttreatment Follow-Up period.

The end of the study will be defined as the date of the clinical database lock (ie, when all study data are collected and data validation is completed).

As required by some regulatory agencies, the following estimates are provided:

- The study will begin in Nov 2014 and will end on or before Aug 2019.
- The maximum estimated period for each subject on study is anticipated to be approximately 2 years.

## 9.2 Discussion of Study Design, Including Choice of Control Groups

### 9.2.1 Overview

The design of this study allows Proof of Concept to be established in subjects with MCI/Prodromal AD. The study also allows investigation of efficacy in subjects with mild AD to determine whether the effects of E2609 in this later stage population are comparable with those established in the MCI/Prodromal population within this same study (see Section 9.2.3 for discussion of the Bayesian design used in this study).

The inclusion criteria for the MCI/Prodromal cohort will be consistent with the NIA-AA criteria for MCI due to AD (Albert, et al., 2011) and with the definition of Prodromal AD per Dubois et al., 2010 (see Section 9.2.2).

There is no active or positive control for this study as at this time, there is no cure for AD, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary efficacy tool for this Proof of Concept study is the composite scale ADCOMS (change from baseline in the derived ADCOMS at 18 months). The ADCOMS (Hendrix, et al., 2012) represents a novel composite approach integrating components of well established tools (ADAS-cog, MMSE, and CDR) to improve sensitivity to disease progression and treatment effects in subjects with AD (see Section 9.2.4).

Secondary efficacy endpoints include a biomarker of neuronal degeneration (shrinkage of neurons), which is the change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI; an amyloid biomarker, which is the change from baseline in CSF Aβ(1-x) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects; and a cognitive and functional assessment, which is the change from baseline in the derived ADCOMS at 18 months of treatment in mild AD subjects. Exploratory endpoints including assessments of efficacy, safety and other biomarkers are also included.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

The rationale for the selection of doses used in the study is provided in Section 9.4.4.

### 9.2.2 Rationale for Study Population

By the time AD progresses to dementia, with loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack, et al., 2010). There is a growing consensus within the AD field that it may be necessary to initiate disease modifying treatments earlier, before the onset of clinical dementia (Aisen, et al., 2010). It is possible that this consideration explains the failure of the humanized monoclonal antibody bapineuzumab (which targeted brain amyloid) to demonstrate clinical efficacy in late-phase studies in mild-to-moderate AD dementia.

The primary patient population of focus in this study is subjects with MCI/Prodromal AD and they will be recruited during both Stage A and Stage B of the study. The mechanism of action of a BACE1 inhibitor where amyloid production is reduced means E2609 is more likely to be efficacious (ie, slow disease progression) the earlier in disease progression treatment is started, where limited neurodegeneration has occurred and associated clinical deficits are at a minimum. Key safety aspects will be assessed in Stage A in which the

MCI/Prodromal AD subjects have less advanced disease compared with subjects with mild AD who will also be recruited in Stage B.

As discussed, efficacy is more likely to be observed in subjects with MCI/Prodromal AD but there is the possibility that efficacy will also be evident following administration of an amyloid modifying agents such as E2609 in subjects with slightly more advanced disease such as mild AD. A study of tarenflurbil, a selective Aβ(1-42)-lowering agent, on cognition and function in subjects with mild to moderate AD showed only the subjects with mild AD had lower rates of decline than those in the placebo group in activities of daily living and global function; however, slowing of cognitive decline did not differ significantly (Wilcock, et al., 2008). Similarly, differential effects on cognitive measures have been observed with solanezumab, where some benefit from treatment was observed in subjects with mild AD but not in subjects with moderate AD, although studies with solanezumab were considered to have failed to improve cognition or functional ability significantly (Doody, et al., 2014). Therefore, it is relevant to compare the effect of the BACE1 inhibitor E2609 in 2 different subject populations that differ in terms of AD severity before the initiation of large Phase 3 clinical studies.

### 9.2.3 Rationale for the Use of Bayesian Adaptive Design

This study uses a Bayesian adaptive design for the MCI/Prodromal cohort only in Stage B. This design optimizes subject allocation and evaluation of efficacy in a smaller number of subjects by maximizing the number of subjects exposed to doses of interest. Frequent interim analyses will be performed to assess the probability of early success and futility and to aid in making early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis, such that subjects are more likely to receive a dose that is efficacious.

Subjects with mild AD recruited in Stage B will be assessed as a "nested" population that does not follow the Bayesian adaptive design. It was not considered appropriate to have a Bayesian design for both cohorts as this would have substantially increased the overall study sample size, delayed analyses of dose response, and would have added background "noise" for the comparison of subjects with MCI/Prodromal AD compared with those with mild AD. Data from each cohort will be analyzed independently for the purposes of decision making. A separate analysis of the 2 cohorts avoids the risk of data from subjects with mild AD confounding the results for the primary population (MCI/prodromal).

### 9.2.4 Rationale for Clinical Endpoints

The ADCOMS (Hendrix, et al., 2012) was developed utilizing data from multiple studies to investigate responsiveness to progression and treatment effects rather than sensitivity to baseline deficits. The score was built empirically with no a priori assumptions, using a partial least squares regression model for placebo data from 4 MCI studies with a duration ≥12 months. A combination of cognitive and functional items was selected from a variety of well-established and validated scales that is most sensitive to change over time. The partial least squares regression coefficients from the model were used to form a weighted composite

score comprising a total of 12 individual items taken from the ADAS-cog (4 items), the MMSE (2 items), and CDR (6 items), that assess both cognition and global function. Performance of the ADCOMS has been assessed against the original scales in several studies. The use of the ADCOMS allows for substantial sample size reductions in non-enriched and enriched MCI populations even over a 12-month period by increasing sensitivity. This derived score has shown adequate sensitivity in the MCI due to AD amyloid confirmed (CSF Aβ-positive) subgroup.

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007).

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The CDR is a clinical global rating scale requiring the interviewing of both the subject and an informant who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The CBB is a brief, computer-administered cognitive test battery that requires approximately 10 minutes for administration (Darby, et al., 2012; Fredrickson, et al., 2008; Maruff, et al., 2009). The CBB has been used to detect cognitive impairment in several neurodegenerative conditions including the measurement of cognitive function in healthy older adults and in adults with clinically diagnosed AD and prodromal AD (Darby, et al., 2009; Hammers, et al., 2012; Lim, et al., 2012a; Lim, et al., 2012b). The administration, scoring, and reporting of the CBB is automated and highly standardized, resulting in cognitive paradigms that have been well-validated in neuropsychological and cognitive studies (Fredrickson, et al., 2008; Maruff, et al., 2009). See Section 9.5.1.3.1 for further details.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al,. 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials on the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson et al., 2011, Lim, et al., 2012a, Lim, et al., 2012b). Data computations indicate

that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with E2609 treatment.

Volumetric magnetic resonance imaging is discussed in Section 9.2.5.4.

### 9.2.5 Rationale for Biomarkers

#### 9.2.5.1 Overall Rationale

The biomarker strategy for this study includes the following aims:

- To establish an amyloid load in the brain at study entry (via the PET eligibility inclusion criterion)
- To evaluate safety (principally by magnetic resonance imaging [MRI])
- To confirm a PD effect in terms of both Aβ in CSF and brain amyloid assessed by PET and to establish that this PD effect is maintained long-term
- To evaluate disease modification through longitudinal assessments of vMRI, amyloid PET, and CSF biomarkers of neurodegeneration (tau and p-tau)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

#### 9.2.5.2 Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect of E2609 on Aβ(1-40) +Aβ(1-42) and other C-terminally truncated Aβ peptides such as Aβ(1-38) through inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using [$^{11}$C]PiB, suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases in CSF Aβ concentrations that are seen in AD are believed to be related to this decrease in brain Aβ availability.

Both total tau (t-tau) and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni and Bhaskar, 2012). CSF tau measurements have been correlated with cerebral atrophy, while their ratios with Aβ42 have provided useful predictors of cognitive decline and progression to dementia due to AD. Rebalancing dysregulated amyloid production early in the process may positively affect the neurodegenerative process and thus affect these markers and benefit the disease trajectory. Therefore, monitoring these markers in conjunction with amyloid imaging may provide further supportive evidence of efficacy.

Baseline levels of Aβ(1-42), tau, and p-tau will also help elucidate the extent of AD pathology at entry to the study and can be combined with baseline levels of *ApoE4* genotyping in addition to the baseline imaging variables to help explain differences in treatment response.

The study will be stratified at randomization for *ApoE4* gene status in order to account for any *ApoE* status by treatment interaction or *ApoE* status by amyloid-related imaging abnormalities risk interaction.

#### 9.2.5.3 Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) to confirm the presence of AD pathology in the brain of subjects with MCI/Prodromal AD or mild AD at entry to the study; and 2) to evaluate the effects of E2609 on amyloid levels in the brain, both by whole brain analysis (the average of 5 to 6 cortical regions) and brain region analysis.

Longitudinal amyloid PET imaging will be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug) as an exploratory measure of the potential disease-modifying effects of E2609. Longitudinal amyloid PET imaging will only be conducted until 18-month PET scans of acceptable quality have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used.

#### 9.2.5.4 vMRI

Volumetric imaging will be used to evaluate the effects of E2609 on rates of atrophy across the different dose groups and to provide support that effective treatment is associated with modification of disease course (secondary endpoint for the MCI/Prodromal population and exploratory endpoint for the Mild AD population). A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. Clinically efficacious doses are predicted to be associated with a slowing in the rate of hippocampal atrophy compared with rates observed in the placebo and non-efficacious dose groups. Treatment effects on left and right hippocampal, whole brain, and total ventricular volumes are exploratory endpoints.

Annualized rates of change of 2% to 3% have been reported for the AD brain compared with 1% in MCI and <1% in age-matched controls (Hua, et al., 2010, Leung, et al., 2010). However, subjects with MCI due to AD-dementia (CSF Aβ <192 pg/ml or positive amyloid imaging) show rates of atrophy comparable to those observed in subjects with AD-dementia (Hua, et al., 2009; Hua, et al., 2010; Leung, et al., 2010; Morra, et al., 2009), supporting the notion that such subjects are on similar trajectories as mild AD-dementia. Lower levels of CSF Aβ42, amyloid positivity on PET imaging, and higher levels of CSF tau in addition to the presence of the *ApoE4* allele have all been associated with greater rates of brain atrophy (Fjell, et al., 2010a; Fjell, et al., 2010b) and will be entered as covariates in various analyses. Hippocampal atrophy has also been shown to predict clinical progression independently of

amyloid levels in the brain (Jack, et al., 2010), and this measure will be entered as a covariate in the analysis of the clinical endpoints along with the aforementioned variables.

Brain volume (total ventricular volume, whole brain, temporal lobe) generally shows a modest correlation with performance on a number of cognitive scales (Hua, et al., 2009; Hua, et al., 2010; Freeborough, et al., 1997; Leung, et al., 2010). Using volumetric analysis performed at 6-month intervals, these relationships and the effects of E2609 treatment will be explored further. Recent advances in analysis software have made structural imaging more sensitive to detect small changes and able to reliably measure rates of atrophy at these intervals, particularly in the posterior parietal and the lateral temporal regions during the early stages of disease (Hua, et al., 2009; Hua, et al., 2010). Given these observations, a demonstration of significant slowing or stabilization in the rate of atrophy in response to treatment, compared with placebo, will offer further support for disease modification.

### 9.2.6 Clinical Risks and Mitigation Strategy

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, and to mitigate clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. These safety aspects include the following:

- Two-stage study design: there will be a pause in recruitment after 60 MCI/Prodromal subjects have been randomized to study drug (Stage A). Only after the safety of E2609 in these first 60 subjects (consisting of up to 12 weeks data for the later subjects and longer dosing periods for the earlier subjects) has been reviewed by the DSMB and considered acceptable, will randomization of further subjects into the study commence (Stage B).
- Immunology-related and infection-related exclusion criteria
- Review of unblinded safety data by an independent DSMB at regular intervals
- Safety criteria for discontinuation of study drug based on CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cell) and other lymphocytes (absolute counts and percentage change from baseline), skin rash, reoccurrence of herpes virus infections including any oral herpes, genital herpes or shingles, other infections, MRI changes, ECGs, and pregnancy.

In addition to the features above, other safety aspects of this study designed to mitigate clinical risk include the following:

- Blinded safety data will be monitored by Eisai at regular intervals during the course of the study
- Routine safety assessments will include the monitoring and recording of all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might indicate signals of possible drug abuse potential will require a detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will

be questioned on the frequency and impact of these events. To assess potential immunomodulatory effects, peripheral blood mononuclear cells (PBMCs) will be collected at baseline, during treatment, and posttreatment.

As per the communication from the Food and Drug Administration (FDA) in Aug 2013, there are concerns that hypopigmentation of the skin and mucous membranes may occur with BACE1 inhibitory drugs. Although no such effects have been seen with E2609 to date, assessments by a reviewing dermatologist will be performed at regular intervals during the study. These assessments will be made centrally, using standardized photography and will specifically include evaluation of any areas of depigmentation or any rash. Dermatological assessments will be supplemented with a specific question to subjects regarding skin changes at each visit. Any such changes could be referred to the central reviewing dermatologist, and to a local dermatologist if needed, for further evaluation. See Section 9.5.1.5.8 for further details.

- Baseline and on-study blood, DNA, and CSF samples will be taken and stored for all subjects. These samples may be tested in the event that a subject develops AEs that warrant further investigation (eg, if a subject develops a treatment-emergent infection) (see Section 9.5.1.2.2).
- Central reading of safety brain MRI assessments (including any MRI evidence of demyelination) will be performed at Screening, at approximately 6-month intervals during the Treatment Phase of the study, and at the final Follow-Up Visit.
- Full neurological examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations. Details of the neurological examination are given in Section 9.5.1.5.9.
- Cognitive decline will be assessed as a safety assessment (ADAS-cog$_{14}$, MMSE, and CBB). Of particular importance will be the assessment of reaction time testing using the detection and identification tasks on the CBB.
- An assessment of suicidality using the C-SSRS will be performed at Screening, Baseline, and at regular intervals during the Treatment Phase and Follow-Up periods of the study (see Section 9.5.1.5.11).
- All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will have at least 2 off-treatment Follow-Up visits (4 and 12 weeks after the last dose of study drug). More frequent safety assessments can be made as unscheduled assessments/visits during the off-treatment Follow-Up period, if clinically indicated.
- An ophthalmic examination will be conducted at Baseline and if the subject experiences visual disturbances during the course of the study (see Section 9.5.1.2.1).

## 9.3 Selection of Study Population

Stage A will randomize 60 eligible MCI/Prodromal subjects at 25 centers in the United States. Stage B will randomize up to an additional 440 eligible MCI/Prodromal subjects at approximately 125 centers globally; the final total number will depend upon whether the

prespecified criteria for either early success or futility are met. In addition, a separate cohort of approximately 200 mild AD subjects will be randomized and dosed during Stage B.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

### 9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD (Albert, et al., 2011) or AD dementia (McKhann, et al., 2011) and is "staged" or classified as either MCI (Stage A and Stage B) or mild dementia (Stage B only) and also complies with the following:

**Required at both Screening and Baseline:**

   a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation
   b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT
   c. FAQ ≤20
   d. MMSE ≥20
2. Amyloid positive PET image based on centralized PET scan reading
3. Male or female, age 50 to 85 years, inclusive at time of consent
4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.
5. If receiving acetylcholinesterase inhibitor (AChEIs) or memantine, must have been on a stable dose for at least 12 weeks before the Baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.

6. Must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization

### 9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or MRI
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (eg, arachnoid cysts) or brain tumors (eg, meningioma).
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could confound the MCI/Prodromal or mild AD diagnosis or could interfere with study assessments or procedures
7. A score of ≥8 on the 15-item Geriatric Depression Scale (GDS) at Screening
8. Abnormally low serum vitamin B12 (<LLN) levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the LLN for the testing laboratory) at Screening
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Subjects with hepatic impairment, with total bilirubin greater than 1.5×upper limit of normal (ULN) or International Normalized Ratio (INR) greater than 1.7 at Screening or Baseline. Subjects with Gilbert's syndrome need not be excluded.
11. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.

12. Any contraindications to lumbar puncture (LP) for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity)
13. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. History of Ig deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
15. Subjects with chronic viral hepatitis
16. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
17. A history of ophthalmic shingles
18. A history of ocular herpes simplex virus (HSV) infection
19. Any live vaccine in the 3 months before randomization.
20. Any active infection within the last 4 weeks prior to randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests conducted at Visit 2 (eg, MMSE, CDR, etc) must be repeated.
21. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
22. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below LLN and confirmed by a repeat test conducted 1 week after the initial test
23. Ig (IgG, IgA, or IgM) levels below the LLN
24. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
25. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate ECGs. A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
26. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
27. Left bundle branch block at Screening or Baseline
28. Persistent heart rate <50 or >100 beats per minute (bpm) at Screening or Baseline

29. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
30. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
31. Type 1 or Type 2 diabetes mellitus that is not well controlled
32. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.
33. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
34. Hypopigmentation conditions (eg, albinism and vitiligo)
35. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
36. Has a "yes" answer to the C-SSRS suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
37. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
38. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
39. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
40. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
41. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation
42. Females who are lactating or pregnant (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or

Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

43. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study treatment period or for-28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study treatment period or for 28 days after study drug discontinuation.
    - Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing or who do not agree to use the same contraceptive during the study treatment period or for 28 days after study drug discontinuation.

      (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).
44. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or not practicing highly effective contraception throughout the study period or for 28 days after study drug discontinuation). No sperm donation is allowed during the study period and for 28 days after study drug discontinuation.

### 9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may discontinue study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to stop study drug or withdraw from the study at any time for any reason.

Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug (see Section 9.1.2.3). Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie. at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB and ISLT) will be conducted. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) after the Early Discontinuation Visit or within ± 8 days of either of the Follow-Up Visits (Visit 19 and Visit 20). Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the Subject Disposition eCRF page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study drug and withdraws from the study at the same time, the ED Visit will be followed (see Section 9.5.5).

Safety-related criteria for discontinuation of study drug include the following:

a. A study drug discontinuation threshold will be set based on absolute counts of CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells). The discontinuation threshold will be set at below the level of the LLN, at a level that represents a greater risk of opportunistic infection in the treated population. For CD4 (T helper cells) the discontinuation threshold is 250 cells/µL. For CD8 (cytotoxic T cells) and CD19 (B cells) the discontinuation thresholds are 150 cells/µL and 50 cells/µL, respectively. Any subject who has CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below the discontinuation threshold as confirmed by a repeat test conducted within 1 week of the initial test will be discontinued from study drug.
b. Subjects with CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between the LLN and the discontinuation threshold will have lymphocyte subset counts performed on a weekly basis. Subjects with a >33% reduction from baseline in CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts will also have lymphocyte subset counts performed on a weekly basis. For these subjects, the decision as to whether the subject remains on study drug or is to be discontinued from study drug will be based upon clinical judgment and will take into account any clinical presentation in addition to the lymphocyte subset counts. These subjects may continue with treatment if there is no clinical evidence of infection. They will be discontinued from study drug if they have infections of a moderate to severe intensity (eg, subjects whose infections are not localized, or are systemically unwell, or who require systemic antiinfective drug treatment).

**Table 1 Study Drug Actions for Lymphocyte Subset Absolute Counts**

| Lymphocyte subset absolute counts | Action | Decision to continue or discontinue |
|---|---|---|
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold | Retest within 1 week | If retest performed within 1 week confirms lymphocyte subset counts below the discontinuation threshold, discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between LLN and discontinuation threshold or >33% reduction from baseline in CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts | Lymphocyte subset counts to be performed weekly until counts return to ≥ LLN or no more than 33% reduction from baseline | Decision will be based upon lymphocyte subset counts and clinical judgment |

LLN = lower limit of normal.

c. Subjects with clinical evidence of infection will have their CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts measured. Blood and other biological samples will also be collected for investigations of infective pathogens (eg,

serological tests, quantitative polymerase chain reaction, microscopy, and culture) where appropriate. In subjects with infection, if any of their absolute cell counts meets the discontinuation thresholds, study drug will be discontinued. All subjects with severe infections will be discontinued from study drug. All subjects with herpes zoster (shingles) or ocular herpes infections will be discontinued from study drug, regardless of severity of presentation. Subjects with mild or moderate infection may continue treatment with study drug unless otherwise clinically indicated or otherwise specified below. Specifically, when any of the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are between the LLN and the discontinuation thresholds or have shown >33% reduction from baseline, subjects with infections of moderate intensity will be discontinued from study drug (eg, subjects whose infections are not localized, or subjects who are systemically unwell, or who require systemic antiinfective drug treatment). All subjects with infection who are discontinued from study drug will be followed for a period of 12 weeks or until the infection resolves/ stabilizes or until the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts have returned to >LLN (whichever comes latest).

**Table 2 Study Drug Actions for Lymphocyte Subset Absolute Counts and Infection**

| Criterion | Severity of Infection | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below discontinuation threshold | Discontinue study drug | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between LLN and discontinuation threshold or >33% reduction from baseline in CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts | May continue treatment with study drug unless clinically indicated | Discontinue study drug | Discontinue study drug |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts always >LLN and no reduction from baseline >33% | May continue treatment with study drug unless clinically indicated | May continue treatment with study drug unless clinically indicated (See (e) for exception) | Discontinue study drug |

LLN = lower limit of normal.

d. A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (see (e) for exception), will be discontinued from study drug and a dermatological consult will be requested regardless of whether the rash is considered drug-related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatological consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

e. Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

f. Development of any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. If discontinued from study drug, subjects will undergo an ED Visit within 7 days after discontinuation and will attend the Follow-Up Visits 4 and 12 weeks after the last dose of study drug. They will also undertake an Unscheduled Visit (with MRI) at approximately 4 weeks after the visit at which such MRI features were first identified. An MRI will also be performed at approximately the time of the second Follow-Up Visit (Visit 20). Additional visits for safety may be arranged if clinically indicated in the opinion of the investigator, including after 12 weeks after the last dose of study drug. At any time during the treatment period, subjects who have asymptomatic, treatment-emergent microhemorrhages as detected by MRI, but none of the features which merit discontinuation of treatment (ie, vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic treatment-emergent microhemorrhage) may continue with treatment. These subjects will have safety assessments (including MRI) at approximately 4 weeks after the visit at which such MRI features were found. They will also continue with the scheduled MRI scans. Additional unscheduled MRI scans may be arranged on an individual subject basis in discussion with the study medical monitor.

g. A postdose ECG with an average QTcF interval >500 msec from triplicate ECGs

h. A postdose ECG with a QTcF interval increase from baseline >60 msec and a QTcF interval >450 msec as demonstrated from triplicate ECGs

i. Any seizure (motor or non-motor)

j. Pregnancy

## 9.4 Treatments

### 9.4.1 Treatments Administered

For this study the test drug is E2609 and the control drug is placebo. All study drugs are to be administered orally, QD, with food. As shown in Figure 1, there will be 4 treatment arms in the MCI/Prodromal Cohort where E2609 will be administered at 3 doses (5 mg, 15 mg and 50 mg) and the comparator is placebo. In the Mild AD Cohort, there will be 3 treatment arms where E2609 will be administered at 2 doses, and the comparator is placebo. The 2 highest E2609 doses (15 mg and 50 mg) taken into Stage B, after the PK/PD and safety review from Stage A for the MCI/Prodromal group, will be used for the Mild AD population.

Study treatment will begin on Day 1 (at the study site) following Randomization and will continue for approximately 78 weeks. Please refer to Table 7 and Section 9.5.1.4.1 for specific information on drug administration on days when PK sampling is to be performed.

Study drug doses will remain the same for each individual subject unless the interim PK/PD analysis determines that an entire dose level requires adjustment (Section 9.4.4). See Section 9.3.3 for safety-related discontinuation criteria of study drug. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a

general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

### 9.4.2 Identity of Investigational Product

E2609 tablets of 5-mg, 10-mg and 25-mg dose strengths will be supplied. Placebo tablets of identical appearance will also be available. Each subject will receive 2 tablets, which combined will make up the required doses of E2609 5 mg, E2609 15 mg, E2609 50 mg, or placebo. The tablets will be supplied by the Sponsor in labeled blister packs. The product release certificates for E2609 and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either E2609 or placebo, or both (see Section 9.4.2.3 for labeling details).

#### 9.4.2.1 Chemical Name and Formula of E2609

- Test drug code: E2609
- Generic name: not applicable
- Chemical name: International Union of Pure and Applied Chemistry
- *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

#### 9.4.2.2 Comparator Drug

Not applicable.

#### 9.4.2.3 Labeling for Study Drug

E2609 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier (ID)
- Lot number/batch number
- Storage conditions, expiration date if necessary

#### 9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

### 9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used for MCI/Prodromal subjects and for mild AD subjects are described in Section 9.4.1.

Randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized blister card identification numbers. At enrollment, the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 3), the IxRS will assign each subject a unique randomization number.

### 9.4.4 Selection of Doses in the Study

It is not known how the level of CSF or brain Aβ reduction is related to clinical efficacy. Therefore, in this study, doses will be selected such that at steady state, they will result in 25%, 50%, and 75% reduction in CSF Aβ levels from baseline to cover a broad range of PD effects.

In Study 007, the relative bioavailability of a tablet formulation of E2609 in the fed and the fasted states compared with the capsule formulation in the fasted state (used in Studies 001 and 002) was investigated. It was found that when the tablet form of E2609 (50 mg) was administered with food, the exposure (ie, AUC) of the parent drug E2609 was higher, with lower maximum observed concentrations and reduced exposure to the metabolites, compared with either formulation in the fasted state.

Based on the PK/PD modeling using data from healthy volunteer Studies 001, 002, and 007, doses of 5 mg, 15 mg, and 50 mg QD administered as the tablet formulation with food in this study should achieve CSF Aβ reduction from baseline of approximately 25%, 50%, and 75% at steady state, respectively (Table 3).

**Table 3 Predicted Steady State Plasma PK Parameters and CSF Amyloid β Reduction From Baseline**

| E2609 Tablet Daily Dose (mg) With Food | E2609 Plasma $C_{max,ss}$ (ng/ml) | E2609 Plasma $C_{ss,av}$ (ng/ml) | E2609 Plasma $AUC_{(0-24h)ss}$ (ng.h/ml) | % Reduction CSF BACE1 Activity | % Reduction CSF Aβ(1-x) |
|---|---|---|---|---|---|
| 5 | 6.2 | 3.3 | 80.3 | 16.2 | 33 |
| 15 | 18.6 | 10 | 240.9 | 36.6 | 56 |
| 50 | 62.1 | 33.5 | 803.0 | 65.7 | 79 |

Aβ(1-x) = amyloid beta monomer from amino acid 1 to x, $AUC_{(0-24h)ss}$ = area under the concentration x time curve at steady state from time zero to 24 hours, BACE1 = Beta-amyloid converting enzyme, CSF = cerebrospinal fluid, $C_{ss,av}$ = average steady-state concentration, $C_{max,ss}$ = maximum plasma concentration at steady state, PK = pharmacokinetics.

The PK/PD modeling described above, which was conducted using data obtained from healthy volunteers, has also been supported by modeling of data from subjects with an underlying AD pathology (Study 101). Furthermore, external data with another BACE1 inhibitor (MK-8931) showed a similar PD effect in AD patients as in healthy volunteers (Forman, et al., 2013). Therefore we are confident that the modeling of E2609 effects in healthy subjects will be applicable for both MCI/Prodromal and Mild AD dementia patients.

The exposure of the highest dose in this study (50 mg QD tablet administered with food) is less than that of the 100 mg QD dose (capsule administered fasted) in Study 002.

The 100 mg QD dose administered for 14 days in Study 002 was well tolerated with no clinically significant changes in laboratory parameters, vital signs, or ECG parameters. On Day 15, for the 100 mg QD cohort in Study 002, there was a reduction of CD4 lymphocyte counts compared with placebo (CD4 lymphocyte counts on E2609 decreased by 3.1% from baseline, whereas the placebo control showed an increase of 8.7%), but this decrease was less than that observed at doses of 200 mg (22.9% decrease) or 400 mg (17.3% decrease). No subjects had infections or drug rash while receiving E2609 100 mg QD or at lower doses in Study 002, whereas at 200 mg and 400 mg QD, 4 subjects had symptomatic orolabial HSV1 relapses and 2 subjects at the highest dose had drug rash. The highest dose for Study 202 of 50 mg QD (tablet administered with food) is therefore expected to have a similar or better safety profile compared with the 100 mg QD capsule (administered fasted) in Study 002. Specific exclusion criteria, blinded and unblinded safety monitoring procedures, and safety criteria for discontinuation from study drug are included in this study in order to mitigate any immunology-related risk with E2609, particularly in light of the progression from 14 days of dosing (Study 002) to 18 months of dosing in this study.

Subjects in the MCI/Prodromal cohort, whether in Stage A or Stage B, will be randomized to receive either placebo or E2609 at 5 mg, 15 mg, or 50 mg QD. Subjects with mild AD (Stage B) will be randomized to receive either placebo or E2609 at 15 mg or 50 mg QD, but not the 5-mg QD dose. The rationale for not including an E2609 5-mg QD dose in the dose regimens for subjects with mild AD is that more advanced disease may require greater reduction in CSF Aβ levels for comparable effects.

After 60 MCI/Prodromal subjects in Stage A have completed 4 weeks of treatment, an interim analysis of the E2609 PK and PD profiles will be used to confirm the E2609 doses to be used for Stage B, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels. If the 95% confidence interval of the mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment with a dose of E2609 does not include its intended target value (ie, 25%, 50%, and 75% reductions from baseline, respectively for E2609 at 5 mg, 15 mg, and 50 mg), PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data from Stage A and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline after 4 weeks of dosing. From this model, the new target plasma steady state concentrations of E2609 required to achieve the target levels of CSF Aβ(1-x) reduction will be estimated again. Dose adjustment for Stage B may be considered if it is possible to get closer to the new target plasma steady state concentrations of E2609 required to achieve the intended target levels of CSF Aβ(1-x) reduction than is possible with the initially planned doses, given the limitation that E2609 dose adjustments will have to be in 5-mg increments or decrements. Subjects already randomized to a dose that needs to be adjusted will be switched to the new adjusted dose and complete their treatment at this new dose.

If dose adjustment is required for Stage B, a protocol amendment reflecting the new doses will be submitted.

### 9.4.5 Selection and Timing of Dose for Each Subject

E2609 is administered orally, QD, with food. Study treatment will begin on Day 1 following randomization and will continue for approximately 78 weeks.

### 9.4.6 Blinding

E2609 and placebo will be administered as tablets of identical appearance.

During the Randomization Phase and Follow-Up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and Eisai staff will be blinded to the treatment codes (double-blind).

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments (ie, those who are trained and certified to perform the various cognitive assessments that are undertaken in this study). Furthermore, at the site, the notes and reports relating to safety assessments must be kept separate from the notes and reports relating to efficacy.

Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

The PK/PD interim analysis to confirm the E2609 doses to be used for Stage B will be conducted by an independent group. Any changes to dose will be reflected in an amendment

to the protocol and the Statistical Analysis Plan will detail how data will be handled in the primary analysis.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

At the conclusion of the study, all unused drug supplies are to be returned to the Eisai approved contract packaging vendor.

### 9.4.7 Prior and Concomitant Therapy

Medication (including over-the-counter medications) or therapy administered to the subject before the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2. Prohibited medications are presented in Listing 1, Listing 2, Listing 3, Listing 4, Listing 5, and Listing 6. Medications that are permitted with restrictions are listed in Listing 7, Listing 8, and Listing 9.

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit:

- Anticoagulants (eg, warfarin, digabatrin) are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization
- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Strong CYP3A4 inhibitors are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization

Subjects taking AChEIs or memantine must meet the following criteria in order to be included in the primary analyses:

- On a stable dose for 12 weeks before the Baseline cognitive assessments at Visit 2
- Remain on a stable dose while on study

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for the primary analyses.

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety, and are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks.

### 9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Phase of the study. CRAs will review treatment compliance during site visits and at the completion of the study.

### 9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study

- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the principal investigator including a copy of the principal investigator's current medical license (required for United States sites) or medical registration number on the curriculum vitae
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and

reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

## 9.5 Study Assessments

### 9.5.1 Assessments

#### 9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

#### 9.5.1.2 Baseline Assessments

Assessments to be made at Screening and Baseline and throughout the study are described in Section 9.5.1.3, Section 9.5.1.4, and Section 9.5.1.5.

##### 9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, current medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment due to AD. Subjects will be asked about history of TB, infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV Types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include onset, duration, relapse frequency, severity, and treatments. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The 15-item GDS and modified Hachinski ischemic scale will also be assessed at Screening as part of the exclusion criteria.

Physical examinations (complete or routine) will be performed as designated in Table 6. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, and skin, and a neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes

from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### 9.5.1.2.2 VIRAL TESTING

As specified in Table 6, blood will be collected for screening for Hepatitis B and Hepatitis C for determining eligibility, and at Baseline for viral characterization.

#### 9.5.1.2.3 B12 TESTING

Blood will also be collected for vitamin B12 levels as specified in Table 6.

#### 9.5.1.2.4 TB EXPOSURE TESTING

Blood will also be collected for testing for previous TB exposure, as specified in Table 6.

#### 9.5.1.2.5 URINE DRUG TESTING

Urine will be collected for drug screening as specified in Table 6.

### 9.5.1.3 Efficacy Assessments

#### 9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

The timing of psychometric assessments is shown in Table 6 and Table 7. These assessments should be administered in the morning (or, if not possible, consistently at the same time of day) and should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The order of assessments is: MMSE, CDR, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall) at Screening; and MMSE, CDR, ADAS-cog$_{14}$, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall) at the Baseline Visit.

At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

**The Derived Alzheimer's Disease Composite Score:** The primary efficacy endpoint is the change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects.

The ADCOMS is derived from the ADAS-cog (4 items), the MMSE (2 items), and the CDR (all 6 items), described below. The ADCOMS is more sensitive to clinical progression compared with currently existing clinical batteries and requires smaller sample sizes for clinical studies in MCI/Prodromal AD or mild AD. It also shows sensitivity to treatment effects with AChEIs. The ADCOMS assesses both cognitive and functional domains and can be offered as a single primary clinical endpoint. The ADCOMS has a range from 0 to 1.97.

**CogState Brief Battery:** The CBB is a computer-based battery comprising 4 cognitive tests:

1. Detection – a simple reaction time test where the subject presses a key when the card is turned face up from a pack of cards ("Has the card turned over"). Speed of response is the measure.
2. Identification – a simple choice reaction time test where the subject presses 1 of 2 keys when the card just turned face up is either a red card or a black card ("Is the card red"). Speed of response is the measure.
3. One Card Back – a simple working memory test where the subject presses 1 of 2 keys when the card turned face up is either the card seen in the immediately previous trial or not ("Is the previous card the same"). Accuracy of response is the measure.
4. One Card Learning – a visual learning and memory test where the subject presses 1 of 2 keys depending on whether the card just turned face up has been seen before or not in the task ("Have you seen this card before in this task"). Accuracy of response is the measure.

**ISLT:** The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 15 minutes, in which time the CBB is performed, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

**Mini Mental State Examination:** A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

**Clinical Dementia Rating:** The CDR assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

**Alzheimer's Disease Assessment Scale - cognitive subscale:** Discussed in Section 9.2.4.

**Functional Assessment Questionnaire:** Either a caregiver or informant or the subject provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

#### 9.5.1.3.2 VOLUMETRIC MRI

Volumetric MRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the Alzheimer's Disease Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume

provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

Volumetric MRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. Volumetric MRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. Volumetric MRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 6 and Table 7, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

CSF samples will be collected by LP (gravity drip method) at the timepoints specified in Table 6 and Table 7. The CSF sample taken at the Baseline Visit will only be performed after confirmation of an amyloid positive PET scan. See Section 9.5.1.4.2 for further details.

### 9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

#### 9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood and CSF samples will be collected for the determination of the concentrations of E2609. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with E2609.

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 6 and Table 7. Two PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visits 5, 11, 14, and 16, and 4 to 8 hours postdose at Visit 7 and Visit 18 (or at the ED Visit). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug with food at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or at the ED Visit) the PK blood sample should be collected shortly after completing the LP. Although the PK sampling procedures at the ED visit should follow those of Visit 18, in the event that study drug has already been discontinued prior to the ED visit, then no dosing will be conducted. However, a PK sample at trough (before LP) will be collected, followed by LP

at approximately the same time as previous visits, and then the post-LP PK sample will be collected.

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

#### 9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

**Biomarkers**

Subjects will be encouraged to stay at the site after completion of LP for medical observation. At Baseline, a CSF sample will be collected by LP (gravity drip method) after fasting (preferred), or at least 2 hours after the most recent meal. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 and Visit 18) can be performed between 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. At visits where cognitive tests are also performed, the LP must be performed after the cognitive tests have been completed; the subjects should rest and drink some fluid to hydrate after the cognitive tests and before the LP. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. The CSF sample will be used for PD assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), t-tau, p-tau, and BACE. The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses (eg, miRNA). Aβ(1-x) in both CSF and plasma will be measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and post-screening analysis of CSF Aβ(1-42), t-tau, and p tau will be performed using ELISAs. BACE1 levels will be measured using internally developed fluorescence resonance energy transfer and ELISA based assay(s). Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

The blood sample collected for PD analyses at Baseline should be collected shortly after completing the LP at Baseline. The sample should be collected at fasting or at least 2 hours after the most recent meal.

At the Baseline Visit, CSF and blood samples will be collected and stored for determination of prior exposure to any suspected infective agents in the event that the subject develops treatment-emergent AEs that warrant further investigation (eg, treatment-emergent infection). Testing may include, but not be limited to, serological tests, viral titer by quantitative polymerase chain reaction, or human leukocyte antigen genotyping.

Blood samples will be collected for PD assessments as specified in Table 6 and Table 7. See Section 9.5.1.4.2 for further details.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

**Pharmacogenomics**

A blood sample will be obtained at Baseline and will be used to determine the *ApoE* genotype (homozygous or heterozygous E4 versus non-E4) and the *NAT2* phenotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response, safety, or PK of E2609. Details of which genotype / phenotype data will be applied to the analyses of efficacy, safety or PK will be discussed in the Statistical Analysis Plan.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

**Amyloid PET**

An amyloid PET scan will be performed at Screening to confirm deposition of amyloid in the brain. Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted until acceptable 18-month PET scans have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used (Table 6). PET scanning will be performed with a locally approved Aβ imaging agent, eg, Amyvid. Descriptions and detailed instructions for all imaging can be found in the imaging manual.

Amyloid PET imaging is an exploratory measure of the potential disease-modifying effects of E2609.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

#### 9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, lymphocyte subsets, Igs, and urine values; periodic measurement of vital signs and ECGs; performance of physical and neurological examinations; centralized dermatological assessments; the C-SSRS; and safety MRIs as detailed in Table 6 and Table 7. will also be conducted. Peripheral blood mononuclear cells (PBMCs) will be collected at Baseline, during treatment, and posttreatment for exploratory immunomodulatory and immune-based analyses.

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments (see Section 9.4.6).

#### 9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E2609.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: It is not necessary to report every sign or symptom as a separate AE if the overall disease [diagnosis] is being reported as an AE.)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, discontinuation of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 20, as shown in Table 7). For subjects who discontinue early from study drug but undertake further efficacy assessments, AEs will only be collected for 3 months after the last dose of study drug, ie, through to the second follow-up visit (Visit 20). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF. SAEs will be collected for 3 months after the last dose of study drug, ie, through to the second follow-up visit (Visit 20). For subjects who discontinue early from study drug but continue with further efficacy assessments, SAEs will be solicited only for 3 months after the last dose of study drug, i.e. up to the 2nd follow up visit (Visit 20). However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the ADCOMS, ADAS-cog$_{14}$, MMSE, and CBB (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 4

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis
- Dissociative state

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.11 for a description of the C-SSRS).

The following adverse events will require the collection of information sufficient to provide a detailed description of the event, treatment and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection; any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a "yes" answer to Type 4 or 5 suicidal ideation, or a "yes" response to any suicidal behavior on the C-SSRS.

All AEs must be followed through the second follow-up visit (Visit 20), or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

**Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.**

### Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

### Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

#### *Classification of Causality*

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

#### 9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reportable using the criteria of important medical event if the event does not meet other serious criteria: new onset seizures, ocular herpes.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the eCRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug

- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

#### 9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 4. Subjects should be in a seated or supine position during blood collection. Table 6 and Table 7 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

See Section 9.3.3 for safety criteria for discontinuation from study drug related to absolute counts of CD4, CD8, and B lymphocytes, and for lymphocyte subset counts.

**Table 4 Clinical Laboratory Tests**

| Category | Parameters |
|---|---|
| **Hematology** | Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), and (Screening and Beseline only), PT, PTT, and INR |
| **Chemistry** | |
| **Electrolytes** | Bicarbonate, calcium, chloride, phosphate, potassium, sodium |
| **Liver function tests** | Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin |
| **Renal function tests** | Blood urea/blood urea nitrogen, creatinine |
| **Other** | Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid |
| **Urinalysis** | Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells |
| **Other** | Lymphocyte subset analyses (see Table 5). Regulatory T cells will be measured using CD4, CD25, and CD127 cell surface markers and FoxP3 intracellular marker.<br>PBMCs<br>Ig analyses (IgG, IgA, and IgM).<br>Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]).<br>Viral characterization (including HSV1, HSV2 and CMV, etc)<br>Serum pregnancy test (females of child bearing potential only)<br>Tuberculosis Interferon Gamma Release Assays<br>Tests for thyroid function (thyroid stimulating hormone, free triidothyronine and free thyroxine) and vitamin B12<br>Blood sample for storage for subsequent testing of immune status<br>Cerebrospinal fluid sampling |

CMV = cytomegalovirus, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV = herpes simplex virus, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononeuclear cell, PT = prothrombin time, PTT = partial thromboplastin time.

The 8 different surface markers (CD3, CD4, CD8, CD45, CD19, CD16, CD56, and CD14) and total lymphocyte counts will be measured in order to provide the lymphocyte subset data as shown in Table 5. In addition, Regulatory T cells will be measured using CD4, CD25, and CD127 cell surface markers and FoxP3 intracellular marker.

**Table 5 Lymphocyte Subtyping**

| Cell Type | Cell Surface Markers |
|---|---|
| T lymphocytes | CD3 |
| T helper cells | CD3+, CD4 |
| Cytotoxic T cells | CD3+, CD8 |
| Mature B cells | CD3-, CD19 |
| Natural killer cells | CD3-, CD16, CD56 |
| Macrophages | CD14 |

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the case report form [CRF] Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

#### 9.5.1.5.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [bpm], respiratory rate [per minute], body temperature [in centigrade], and weight [kg]) will be obtained at the visits designated in Table 6 and Table 7 by a validated method. Measurements of sitting BP and heart rate will be obtained. All BP measurements should be performed on the same arm, preferably by the same person.

#### 9.5.1.5.5 Physical Examinations

A complete physical examination will be performed at Screening as described in Section 9.5.1.2.1. At Baseline and during the Randomization Phase, routine physical examinations will take place as shown in Table 7. These examinations will include the cardiovascular system, respiratory system, and neurological system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.6 Electrocardiograms

Electrocardiograms will be obtained as designated in Table 6 and Table 7. Twelve-lead standard ECGs will be recorded in triplicate (1 minute apart) after subjects have been resting in the supine position for at least 5 minutes.

On any study day when ECG, vital signs, and blood samples are taken, these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.7 SAFETY MRI

Safety brain MRI assessments will be performed at the times shown in Table 6 and Table 7. Additional safety MRI scans can be performed at unscheduled visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Safety MRIs will be acquired using a standardized procedure that will include fluid-attenuated inversion recovery (FLAIR), gradient-echo, T1, and diffusion-weighted sequences to determine the presence of focal lesions including, but not limited to, evidence for ischemic and hemorrhagic stroke, subdural hematoma, neoplasm, arteriovenous malformation, micro and macrohemorrhages, superficial siderosis, lacunar infarcts, white matter abnormalities, and vasogenic edema. The imaging sequence for the Screening/safety MRI will include: T2 weighted anatomic MRI to rule out major white matter changes, cerebral infarction or other structural lesions, and a high-resolution 3D T1-weighted scan with isotropic voxels with volumes of 1 $mm^3$ or less. In addition, both FLAIR for the detection of vasogenic edema and T2* Gradient Recall Echo for the detection of microhemorrhages will be acquired. The 3D dataset will be reconstructed in transverse slices in Digital Imaging and Communications in Medicine format. The results of this MRI assessment will also be used as the Baseline Period MRI, against which changes after drug administration will be compared. Further details of the MRI protocol can be found in the Imaging Acquisition Guideline. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, and 18 and at the second Follow-Up Visit (Visit 20). In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

At any time during the treatment period, subjects will be discontinued from study drug if they develop any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. All of these features must be reported as study specific AEs (or AEs of special interest). These subjects will undergo an ED Visit within 7 days after discontinuation and Follow-Up Visits at 4 weeks and 12 weeks after the last dose of treatment. Subjects will also undertake an Unscheduled Visit (with MRI) at approximately 30 days after the visit at which such MRI features were first

identified. Additional visits may be arranged if clinically indicated in the opinion of the investigator, and may occur later than 12 weeks after the final dose of study drug.

#### 9.5.1.5.8 DERMATOLOGICAL ASSESSMENT

Centralized skin assessments, using standardized photography, will be conducted by a reviewing dermatologist at the times shown in Table 6 and Table 7. These assessments will specifically include evaluation of any areas of depigmentation or any rash.

In addition, subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregiver or informants will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or infection, and the investigator will be required to review such AEs as soon as possible and consider an unscheduled physical and dermatological evaluation. Detailed characteristics of any skin rashes will be captured in the clinical database. Physical examination may be undertaken where indicated. Treatment-emergent abnormal dermatological findings should be reported as AEs.

#### 9.5.1.5.9 NEUROLOGICAL EXAMINATION

Neurological examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations as shown in Table 6 and Table 7. Details of these examinations will be captured in an eCRF. The neurological examinations will monitor for new symptoms and signs which will then alert the investigator to consider new CNS pathology (especially slowly-evolving neurological conditions that may not lead to prominent symptoms). Examples of neurological signs that may indicate new CNS pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. In such a situation, the investigator should consider (but not limited to) demyelination in the differential diagnoses, and should discuss with the sponsor's medical monitor further investigations or treatment, which will be decided case by case. Neurological examinations will also include the assessment of cranial nerve function, especially the olfactory nerve. Treatment-emergent abnormal neurological findings should be reported as AEs.

#### 9.5.1.5.10 PREGNANCY TEST

At Screening, females of childbearing potential will have a serum pregnancy test. At Baseline and during the Treatment Phase, urine samples will be obtained from females of childbearing potential for pregnancy tests (see Table 7).

#### 9.5.1.5.11 COLUMBIA SUICIDE SEVERITY RATING SCALE

An assessment of suicidal ideation and behavior using the C-SSRS will be performed at the designed time points in Table 6 and Table 7. A "yes" answer to Type 4 or 5 suicidal ideation or a "yes" response to any suicidal behavior queries will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

#### 9.5.1.5.12 BIOMARKER SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be used for exploratory biomarker analyses, as well as tested in the event that a subject develops AEs that warrant further investigation.

#### 9.5.1.5.13 OPHTHALMIC EXAMINATIONS

An ophthalmic examination will be conducted at Baseline (unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available). An additional examination will be conducted, if the subject experiences visual disturbances during the course of the study or is medically indicated. The ophthalmic examinations should include fundoscopy to look at the optic disc, macula and the rest of the retina, as well as an assessment of visual acuity and visual fields.

### 9.5.2 Schedule of Procedures/Assessments

#### 9.5.2.1 Schedule of Procedures/Assessments

Table 6 presents the Schedule of Procedures/Assessments for the Prerandomization Phase. Screening assessments will be organized into 4 tiers (see below and Figure 2).

Table 7 presents the Schedule of Procedures/Assessments for the Randomization Phase.

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

| Phase | Prerandomization | |
|---|---|---|
| **Period** | **Screening** | **Baseline** |
| **Visit** | **1** | **2** |
| **Procedures/ Assessments (to be completed in a maximum of 50 days)** | | |
| Informed consent (subject and caregiver or informant) | X (Tier 1) | |
| Demographics | X (Tier 1) | |
| Medical history[a] | X (Tier 1) | |
| Prior / concomitant medications[b] | X (Tier 1) | X |
| Vital signs including weight[c] | X (Tier 1) | X |
| Height | X (Tier 1) | |
| Complete physical examination | X (Tier 1) | |
| Routine physical examination | | X |
| CBB and ISLT[d] | X (Tier 1) | X |
| MMSE[d] | X (Tier 1) | X |
| CDR[d] | X (Tier 1) | X |
| FAQ[d] | X (Tier 1) | X |
| ADAS-cog14[d] | | X |
| 15-item Geriatric Depression Scale | X (Tier 2) | |
| Modified Hachinski ischemic scale | X (Tier 2) | |
| C-SSRS | X (Tier 2) | X |
| 12-lead ECG[e] | X (Tier 2) | X |
| Blood and urine for clinical laboratory tests[f] | X (Tier 2) | X |
| Blood for lymphocyte subset analyses[g] | X (Tier 2) | X |
| Blood for Ig analyses[h] | X (Tier 2) | X |
| Blood for viral screen[i] | X (Tier 2) | |
| Blood for thyroid function tests[j] | X (Tier 2) | |
| Blood for vitamin B12 test | X (Tier 2) | |
| Test for previous TB exposure | X (Tier 2) | |
| Urine drug screen | X (Tier 2) | |
| Serum pregnancy test (females of childbearing potential only) | X (Tier 2) | |
| Urine pregnancy test (females of childbearing potential only) | | X |
| Safety and Volumetric MRI[k] | X (Tier 3) | |
| Amyloid PET scan[l] | X (Tier 4) | |
| Inclusion and Exclusion criteria | X (All tiers) | X |
| Adverse events | X (All tiers) | X |
| CSF sampling for PK, PD and storage[m] | | X |
| Blood sample for PK assessments[n] | | X |
| Blood sample for PD and exploratory biomarker assessments[o] | | X |
| Blood sample for pharmacogenomics | | X |
| Blood sample for storage for immune status[p] | | X |
| Blood sample for PBMC isolation | | X |
| Blood sample for viral characterization[q] | | X |
| Centralized dermatological assessment via photography[r] | | X |
| Neurological examination[s] | | X |
| Ophthalmic assessment[t] | | X |

## Notes for Table 6

AchEI = acetylcholinesterase inhibitor, AD = Alzheimer's disease, ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CDR = Clinical Dementia Rating, CMV = cytomegalovirus, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), Ig = immunoglobulin, INR = Inernational Normalized Ratio, ISLT = International Shopping List Task (immediate and delayed recall), LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetics, PET = positron emission tomography, PT = prothrombin time, PTT = partial thromboplastin time,TB = tuberculosis.

Note: Screening assessments/procedures have been organized into 4 distinct tiers. All assessments and procedures in each tier should be completed (see Figure 2), and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Similarly, all screening assessments and procedures must be completed, and eligibility to continue in the study confirmed, before any baseline assessments and procedures commence. Adverse events and eligibility against inclusion and exclusion criteria must be assessed at each stage within the Screening Visit and at the Baseline Visit.

Note: All screening and baseline assessments are to be completed within 50 days. The interval between availability of the results of the last screening assessment (PET scan) and the first baseline (Visit 2) assessments should be as short as possible and ideally should not exceed 7 days. Visit 3 (Randomization) (see Table 7) should occur 7 to 10 days after completion of the Baseline visit (Visit 2) and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion #19 into account. Thus, the total Prerandomization Phase may be up to 60 days.

a: To include: mild cognitive impairment and AD history; history of TB, vaccination history against and infections due to varicella zoster virus (chickenpox and herpes zoster or shingles); infections due to HSV1 (orolabial herpes or cold sores) and 2 (genital herpes). Medical history of infections to include: onset, duration, relapse frequency, severity, and treatments.

b: Prior and concomitant medications include AChEIs and memantine, and other medications for cognitive decline.

c: Weight, respiratory rate, body temperature, and sitting blood pressure and heart rate will be obtained.

d: To be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). The order of assessments is: MMSE, CDR, FAQ, ISLT (immediate recall), CBB, ISLT (delayed recall), and CBB (repeat CBB for additional practice) at Screening; and MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall) at the Baseline Visit. At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

e: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

f: Clinical laboratory tests consist of hematology (including PT, PTT, and INR), clinical chemistry, and urinalysis.

g: Lymphocyte subsets to be measured include CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cells), CD16/CD56 (natural killer cells) and CD14 (macrophages). Regulatory T cells will also be measured (CD4, CD25, and CD127, FoxP3). Viability staining may also be employed.

h: Igs to be analyzed include IgG, IgA and IgM.

i: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

j: Thyroid function tests include thyroid stimulating hormone, free triidothyronine and free thyroxine.

k: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images in addition to sequences for resting state functional MRI. MRI will be read by an approved central reader. Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session.

l: PET scanning will be performed with a locally approved β-amyloid imaging agent, eg, Amyvid if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. The PET image will be centrally read for the purpose of determining eligibility for inclusion into the study.

m: CSF will be collected by LP after fasting (preferred), or at least 2 hours after the most recent meal. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 and Visit 18) can be performed at a similar time of day (±1 hour) for each individual subject. The LP must be performed after the cognitive tests have been performed; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. The CSF sample will be used for PK and PD assessments. A CSF sample will also

be stored for testing in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection).

n: The PK blood sample should be collected shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal.

o: The PD and exploratory biomarker blood sample should be collected shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal.

p: A blood sample will be collected at Baseline and stored. This sample may be used for exploratory biomarkers associated with study drug or disease, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

q: Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

r: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. See Section 9.5.1.5.8 for further details.

s: To be performed by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations. Section 9.5.1.5.9 details what is included in the neurological examination.

t: An ophthalmic examination will be conducted at Visit 2 unless the subject has had a comprehensive eye exam within the past 12 months, from which a report is available. The ophthalmic examination should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields.

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| **Phase** | **Randomization** | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | | | | | **Follow-Up** | | |
| **Visit**[a] | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **ED**[b] | **19**[c] | **20**[c] | **UNS Visit**[d] |
| **Day** | **1** | **8** | **15** | **22** | **29** | **43** | **57** | **71** | **85** | **113** | **141** | **183** | **274** | **365** | **456** | **547** | | **575** | **631** | |
| **Week** | **1** | **2** | **3** | **4** | **5** | **7** | **9** | **11** | **13** | **17** | **21** | **27** | **40** | **53** | **66** | **79** | | **83** | **91** | |
| **Weeks elapsed since first dose** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **10** | **12** | **16** | **20** | **26** | **39** | **52** | **65** | **78** | | **82** | **90** | |
| **Nominal months elapsed since first dose** | **0** | | | | **1** | | **2** | | **3** | **4** | **5** | **6** | **9** | **12** | **15** | **18** | | **19** | **21** | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | |
| Routine physical examination | X | | | | X | | X | | X | | | X | X | X | X | X | X | X | X[e] | X |
| Inclusion and Exclusion criteria | X | | | | | | | | | | | | | | | | | | | |
| Vital signs[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[e] | X |
| Respiratory rate | | | | | X | | X | | X | X | X | X | X | X | X | X | X | X | X[e] | X |
| Weight | | | | | | | | | X | | | X | X | X | X | X | X | | X | X |
| Centralized dermatological assessment via photography[g] | | | | | | | | | X | | | X | X | X | X | X | X | | X | X |
| Neurological examination[h] | | | | | | | | | | | | X | | X | | X | X | X | X | X |
| Ophthalmic examination[i] | | | | | | | | | | | | | | | | | | | | X |
| Concomitant medications[j] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG[k] | | | X | | X | | X | | X | | | X | | X | | X | X | X | X[e] | X |
| Clinical biochemistry and urinalysis | | | X | | X | | X | | X | | | X | X | X | X | X | X | X | X[e] | X |
| Complete blood count | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[e] | X |
| Blood samples for lymphocyte subset analyses[l] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[e] | X |
| Blood samples for Igs[m] | | | | | X | | X | | X | | | X | | X | | X | X | X | X[e] | X |
| Blood samples for isolation of PBMCs | | | X | | | | | | X | | | | | | | | | | X | |
| Urine pregnancy test (females of CBP only) | X[n] | | | | | | | | X | | | X | X | X | X | X | X | X | | X |
| Blood sample for storage for immune status[o] | | | | | X | | | | X | | | X | | X | | X | X | X | X | X |
| CBB and ISLT[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| MMSE[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| CDR[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| ADAS-cog$_{14}$[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| **Phase** | **Randomization** | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | | | | | **Follow-Up** | | |
| **Visit**[a] | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **ED**[b] | **19**[c] | **20**[c] | **UNS Visit**[d] |
| **Day** | **1** | **8** | **15** | **22** | **29** | **43** | **57** | **71** | **85** | **113** | **141** | **183** | **274** | **365** | **456** | **547** | | **575** | **631** | |
| **Week** | **1** | **2** | **3** | **4** | **5** | **7** | **9** | **11** | **13** | **17** | **21** | **27** | **40** | **53** | **66** | **79** | | **83** | **91** | |
| **Weeks elapsed since first dose** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **10** | **12** | **16** | **20** | **26** | **39** | **52** | **65** | **78** | | **82** | **90** | |
| **Nominal months elapsed since first dose** | **0** | | | | **1** | | **2** | | **3** | **4** | **5** | **6** | **9** | **12** | **15** | **18** | | **19** | **21** | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | |
| FAQ[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| C-SSRS | | | | | X | | X | | X | | | X | X | X | X | X | X | X | X[y] | X |
| Safety and Volumetric MRI[q] | | | | | | | | | | | | X | | X | | X | X | | X | X |
| Amyloid PET[r] | | | | | | | | | | | | | | | | X | X | | | |
| Telephone contact[s] | | | X | | X | | | | X | | | X | | X | | X | X | | | X |
| Blood samples for PK[t] | | | X | | X | | | | X | | | X | | X | | X | X | | | X |
| Blood samples for PD and exploratory biomarkers[u] | | | X | | X | | | | X | | | X | | X | | X | X | X | X | |
| CSF sampling for PK and PD[v] | | | | | X | | | | | | | | | | | X | X | | | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Sleep/dream questionnaire[w] | | | | | | | | | | | | | | | | | | | | X |
| Randomization | X | | | | | | | | | | | | | | | | | | | |
| Dispense study drug[x] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |

## Notes for Table 7

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating scale, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), Ig = immunoglobulin, ISLT = International Shopping List Task, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, UNS = unscheduled.

a: Visit 3 should be conducted 7 to 10 days after completion of the Baseline visit (Visit 2) assessments and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion #19 into account. A window of ±3 days will be permitted for Visit 4 to 14 inclusive. A window of ±10 days will be permitted for Visit 15 to 18 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since first dose" at subsequent visits.

b: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 19 and Visit 20, respectively). Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie. at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, FAQ, CBB, and ISLT) will be conducted. Regularly scheduled clinical efficacy visits do not need to be attended if they fall within 8 days (visit window) after the Early Discontinuation Visit or within ± 8 days of either of the Follow-Up Visits (Visit 19 and Visit 20). Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above.

c: All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 19 and Visit 20 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up period.

d: Unscheduled visits may be conducted at any time that safety or safety MRI data indicate per protocol or as clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

e: Only if clinically significant abnormalities are found at Visit 19 and the investigator considers it necessary to repeat at Visit 20. However, lymphocyte subsets and Igs should be repeated at Visit 20 if they were outside of the normal range (regardless of clinical significance) at Visit 19.

f: Measurements of body temperature and sitting blood pressure and heart rate will be obtained.

g: Centralized skin assessments using standardized photography will be conducted by a reviewing dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. Additional UNS dermatological assessments should be conducted in response to any dermatological AEs of concern, eg, depigmentation, rash, herpetic lesion.

h: Examples of neurological signs that may indicate new central nervous system pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

i: If the subject experiences visual disturbances during the course of the study, the subject will be referred to a specialist for a further ophthalmic examination, which should include fundoscopy to look at the optic disc, macula and the rest of the retina as well as an assessment of visual acuity and visual fields

j: Please refer to Section 9.4.7, which details prohibited and permitted medications in the study and associated timeframes.

k: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

l: Lymphocyte subsets to be measured include CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [NK cells] and CD14 [macrophages]) and total lymphocytes. Regulatory T cells will also be measured (CD4, CD25 and CD127, FoxP3). Viability staining may also be employed.

m: Igs to be analyzed include IgG, IgA, and IgM.

n: An additional assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

o: Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

p: These assessments are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The order of assessments will be: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). At visits where the CDR or FAQ are conducted, the investigator will determine whether the informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

q: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images in addition to sequences for resting state functional MRI. MRI will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, and 18 and 20. In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A volumetric MRI sequence will be collected in all subjects immediately following all safety MRI assessments.

r: PET scanning will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks.

s: Site staff will contact the subject or the caregiver or informant the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the caregiver or informant, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

t: Two plasma PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visit 5, Visit 11, Visit 14 and Visit 16 and 4 to 8 hours postdose at Visit 7 and Visit 18 (or ED). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or ED) the PK blood sample should be collected shortly after completing the LP. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected, followed by LP at approximately the same time as at previous visits, and then another PK sample shortly after the LP.

u: PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day. At Visits 5, 11, 14, and 16 the PD blood samples should be collected predose.

v: All visits at which CSF samples are scheduled to be taken also include blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Baseline LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. The LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months.

w: Subjects reporting adverse events relating to abnormal dreams, nightmares, or sleep terror will be questioned on the frequency and impact of these events.

x: The first dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time for post-dose medical observation.

#### 9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 6 and Table 7 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 4 tiers (see Table 6, Section 9.1.1.1, and Figure 2.

See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 8 presents the number of blood and CSF samples, and the total volume of blood and CSF that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety.

**Table 8 Summary of Blood and CSF Sample Volumes**

| Assessment | Total number of collection time points | Number of time points x volume per collection (mL whole blood or CSF) | | Total volume (mL whole blood or CSF) |
|---|---|---|---|---|
| | | Screening and Baseline Periods | Treatment and Follow-Up Periods | |
| **Blood** | | | | |
| Chemistry | 12 | 2 x 2 mL | 10 x 2 mL | 24 mL |
| Hematology | 18 | 2 x 5 mL | 16 x 5 mL | 90 mL |
| Lymphocyte subset analyses | 18 | 2 x 4 mL | 16 x 4 mL | 72 mL |
| PBMC | 4 | 1 x 16 mL | 3 x 16 mL | 64 mL |
| IgA, IgM, IgG | 9 | 2 x 2 mL | 7 x 2 mL | 18 mL |
| PT, PTT for INR | 2 | 2 x 3 mL | None | 6 mL |
| Thyroid function tests (thyroid stimulating hormone, free triidothyronine and free thyroxine) | 1 | 1 x 3 mL | None | 3 mL |
| Viral screen (Hepatitis B and C) | 1 | 1 x 4 mL | None | 4 mL |
| Viral characterization | 1 | 1 x 4 mL | None | 4 mL |
| Vitamin B12 | 1 | 1 x 2 mL | None | 2 mL |
| Serum pregnancy test | 1 | 1 x 2 mL | None | 2 mL |
| Tuberculosis (interferon-gamma release assays) | 1 | 1 x 3 mL | None | 3 mL |
| Sample for immune status | 8 | 1 x 4 mL | 7 x 4 mL | 32 mL |
| PD sample | 9 | 1 x 4 mL | 8 x 4 mL | 36 mL |
| PK analysis | 7 | 1 x 3 mL | 6 x 6 mL | 39 mL |
| Pharmacogenetic sample | 1 | 1 x 3 mL | None | 3 mL |
| All blood samples, total volume whole blood collected | | 80 mL | 322 mL | 402 mL |
| **CSF** | | | | |
| PD and PK samples | 3 | 1 x 12 mL | 2 x 12 mL | 36 mL |

CSF = cerebrospinal fluid, Ig = immunoglobulin, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetic, PT = prothrombin time, PTT = partial thromboplastin time.

### 9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include vital signs, clinical laboratory assessments, physical examinations, ECG measurements, and reports of AEs. MRI will be used to detect vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage and is a standard evaluation to ensure subject safety. The C-SSRS has been endorsed by the FDA as a measure of potential suicidality (Guidance for Industry Suicidality).

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, in addition to mitigating clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. Details are provided in Section 9.2.6.

### 9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

#### 9.5.4.1 Reporting of Serious Adverse Events

**All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.**

SAEs, regardless of causality assessment, must be collected up to 3 months after the last dose of study drug, ie, through to the second follow-up visit (Visit 20). In subjects who discontinue study drug early, but continue with efficacy assessments, SAEs only need to be solicited up to 3 months after the last dose of study drug. However, any SAEs volunteered by subjects after this time point must be reported according to standard procedures. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

**For urgent safety issues**, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

#### 9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must discontinue study treatment.

#### 9.5.4.3 Reporting of Events Associated with Special Situations

##### 9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

| | |
|---|---|
| Overdose | Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose |
| Misuse | Intentional and inappropriate use of study drug not in accordance with the protocol |
| Abuse | Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects |
| Medication error | Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject |

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

#### 9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2) should always be considered serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

### 9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

### 9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

#### 9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

### 9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue study drug or withdraw from the study at any time for any reason. All subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 19 and Visit 20, respectively) (see Section 9.1.2.3). See Table 7 for full details of the assessments to be performed at these visits. Subjects who discontinue study drug prematurely will also be scheduled to return to the study site for each scheduled visit when clinical efficacy assessments are to be conducted (ie, at Visits 11, 14, 15, 16, 17, and 18, if these visits have not already been performed). At these visits, only clinical efficacy assessments (MMSE, CDR, ADAS-cog14, FAQ, CBB and ISLT) will be conducted. Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled clinical efficacy visits as outlined above. Subjects who discontinue study drug early (as opposed to subjects whose dosing with study drug is temporarily suspended under Medical Monitor guidance) will not be permitted to restart study drug.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and will provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who withdraw prematurely from the study will be withdrawn for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for withdrawal from the study. Study disposition information will be collected on the Subject Disposition eCRF.

A subject removed from the study for any reason may not be replaced.

### 9.5.6 Abuse or Diversion of Study Drug

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Potential Abuse-related Medication Handling Event eCRF.

### 9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

## 9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

### 9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

### 9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy assessments performed in this study.

## 9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, except for the Bayesian methods on the primary endpoint.

### 9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the statistical analysis plan, which will be finalized before the first interim efficacy analysis.

#### 9.7.1.1 Study Endpoints

See Section 9.2.3 for a discussion of the rationale for the selection and clinical relevance of the primary study endpoint. Further information on the derived ADCOMS is described in Section 9.5.1.3.1.

##### 9.7.1.1.1 PRIMARY ENDPOINT

- Change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects

##### 9.7.1.1.2 SECONDARY ENDPOINTS

Change from baseline in:

- Total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- CSF Aβ(1-x) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
- The derived ADCOMS at 18 months of treatment in mild AD subjects

##### 9.7.1.1.3 EXPLORATORY ENDPOINTS

Change from baseline in:

- The derived ADCOMS at 12 months of treatment in MCI/Prodromal and mild AD subjects
- Total hippocampal volume at 12 and 18 months of treatment in mild AD subjects as measured by vMRI
- CSF Aβ(1-42) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
- CSF Aβ(1-x) and Aβ(1-42) after 4 weeks and 18 months of treatment in mild AD subjects
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ in MCI/Prodromal and mild AD subjects
- CSF biomarkers of neurodegeneration (eg, tau and p-tau) at 18 months of treatment in MCI/Prodromal and mild AD subjects
- Plasma and CSF amyloid, and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild AD subjects
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and, 18 months in MCI/Prodromal and mild AD subjects as measured by vMRI
- Brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild AD subjects
- The population PK parameters of E2609 including the effect of intrinsic and extrinsic factors (including *NAT2* phenotype) in MCI/Prodromal and mild AD subjects

#### 9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol (PP) Analysis Set is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

#### 9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: The number (percent) of randomized and treated subjects who completed the study and who withdrew from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and withdrew from the study. The primary reasons for discontinuation from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

Completion of Study Treatment: The number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for discontinuation from the study drug are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, inadequate therapeutic response, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

#### 9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, MMSE and FAQ; categorical variables include sex, age group (≤65 years, age >65 years), race, ethnicity, *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI/Prodromal AD or mild AD).

#### 9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term. Prior medications will be defined as medications that stopped

before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up period will also be recorded.

#### 9.7.1.6 Efficacy Analyses

***MCI/Prodromal Cohort***

The study in the MCI/Prodromal cohort is based on Bayesian adaptive design. Frequent interim analyses will be performed to assess the probability of early success and futility and to make early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis. Key definitions relevant to the Bayesian aspects of the adaptive design are given below.

**Study Definitions**

- **Maximum Effective Dose ($d_{Max}$):** The dose that achieves the greatest treatment effect.
- **$ED_{90}$:** The lowest dose that achieves at least 90% of the $d_{Max}$ treatment effect in the derived ADCOMS.
- **Early Success:** The study in the MCI/Prodromal cohort will meet early success criteria if the probability that the $ED_{90}$ at 18 months of treatment achieves 25% improvement over placebo is at least 80%. Early success is achieved before all MCI/Prodromal subjects complete 18 months of treatment and can only be determined after at least 200 MCI/Prodromal subjects have been randomized. If early success is declared before full randomization, the randomization of new MCI/Prodromal subjects will stop but subjects already randomized into the study will receive the full 18 months of treatment (following confirmation from the Sponsor's Senior Management).
- **Futility:** The study in the MCI/Prodromal cohort will meet statistical futility criteria if the probability that the $ED_{90}$ is better than placebo by the clinically significant difference of 25% is less than 5% at 18 months of treatment. The statistical futility boundary is binding; if the statistical futility boundary is crossed the study will be considered to have failed.
- **Study Success:** The study in the MCI/Prodromal cohort will be considered a success if an $ED_{90}$ at 18 months treatment has at least an 80% probability of achieving 25% improvement over placebo at either an interim analysis or at the final analysis.

***The Mild AD Cohort***

The analysis of the Mild AD cohort is based on the group sequential design. Interim analyses in the Mild AD cohort will only be performed after the MCI/Prodromal cohort

crosses the early success boundary. The early efficacy signal based on the change from baseline of ADCOMS at 18 months is defined as crossing the interim-analysis boundaries for overwhelming efficacy in the mild AD population. The O'Brien-Fleming (OF) boundaries based on Lan-DeMets alpha spending function will be used to assess overwhelming efficacy. The corresponding OF boundaries based on *P* values will be 0.076, 0.0221, and 0.0423 for the first, second, and final analyses, respectively, according to 2 planned interim analyses at the 60% and 80% information fraction.

#### 9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

***Primary analysis of primary endpoint***

The primary analysis will be based on MCI/Prodromal subjects from the FAS with the prespecified censoring rule applied. The primary endpoint is the change from baseline to 18 months in the derived ADCOMS. The dose-response of the primary endpoint is modelled with a first-order normal dynamic linear model, where Normal and Inverse-Gamma priors are used. The primary efficacy analysis will calculate the Bayesian posterior probability that the dose identified is the most likely $ED_{90}$ dose that achieves 25% improvement over the placebo arm. At each interim analysis and the final analysis, 2 Bayesian probabilities will be summarized for each active dose: the probability it is the $ED_{90}$ dose and the probability of achieving 25% improvement over the placebo arm.

For the clinical efficacy data (ie, derived ADCOMS, MMSE, CDR, ADAS-cog, CBB, ISLT, and FAQ) subjects will be censored at the time of initiation of treatment with AChEIs or memantine, if they were not on these medications at the time of Baseline cognitive assessment (Visit 2), and will be censored at the time of dose adjustment of AChEIs or memantine if they were already on stable treatment with these medications at the time of Baseline cognitive assessment (Visit 2). The value of the primary endpoint for censored subjects will be imputed using data up to the censoring time and Bayesian longitudinal modeling.

***Sensitivity analysis of primary endpoint***

After unblinding, the primary endpoint will be analyzed using the Bayesian methods described above as well as conventional statistical methods. The following additional Bayesian analyses will be conducted as sensitivity analyses:

- The primary endpoint will be analyzed regardless of initiation of treatment, or dose adjustment, with AChEIs or memantine using the same Bayesian analysis method as primary analysis. This is an intent-to-treat analysis without any censoring.
- In case of early success, the primary analysis as well as the above sensitivity analyses will be repeated after all subjects have completed 18 months of treatment or have been lost to follow-up.

Statistical methods for the final conventional analyses will use a mixed-effects model with repeated measures (MMRM) on the change from baseline in the derived ADCOMS at

18 months. The model will include treatment groups, randomization stratification variables (the presence or absence of ongoing treatment with AChEIs or memantine or both, and *ApoE4* status), and baseline ADCOMS as covariates. Other covariates such as adjusted hippocampal volume will be studied. These analyses will be performed as sensitivity analyses on the FAS as well as the PP set and as such, no multiplicity adjustments will be made to account for the interim analyses. In case of early success, the conventional analyses will also be performed using the data collected before the interim analysis.

#### 9.7.1.6.2 SECONDARY EFFICACY ANALYSES

***The MCI/Prodromal Cohort***

An MMRM will be used to analyze the following secondary endpoints:

- Change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-x) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects. Data from early discontinuations will also be included.

Comparisons between each treatment group and placebo will be performed.

***The Mild AD Cohort***

The MMRM will be used to analyze the change from baseline of derived ADCOMS at 18 months in mild AD. If there is no treatment group-by-population interaction in the overall study, the MMRM analysis will include all subjects (MCI/Prodromal or mild AD) in the overall study. Otherwise, the MMRM analysis will only include subjects in the mild AD cohort. The comparison between placebo and active doses will be performed within mild AD subjects regardless of subjects included in the MMRM analysis. Dunnett's method will be used to control for multiplicity due to multiple comparisons.

#### 9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in the derived ADCOMS at 12 months in MCI/Prodromal and mild AD subjects
- Change from baseline in total hippocampal atrophy at 12 and 18 months in mild AD subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-42) after 4 weeks and 18 months in MCI/Prodromal subjects. Data from early discontinuations will also be included.
- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) after 4 weeks and 18 months in mild AD subjects. Data from early discontinuations will also be included.

- Change from baseline in the clinical assessments: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months in MCI/Prodromal and mild AD subjects
- Change from baseline in plasma and CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild AD subjects
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and 18 months as measured by vMRI in MCI/Prodromal and mild AD subjects

A linear mixed-model will be used to analyze the following exploratory endpoints:

- Change from baseline in brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild AD subjects
- Change from baseline in CSF biomarkers of neurodegeneration (eg, tau, p-tau) at 18 months of treatment in MCI/Prodromal and mild AD subjects

Data from early discontinuations will also be used as appropriate. Comparisons between each treatment group and placebo will be performed.

A linear mixed-model with repeated measures will be used to determine the relationship between the following endpoints:

- Change from baseline in the derived ADCOMS score and the change from baseline in biomarkers in CSF at 18 months in MCI/Prodromal and mild AD subjects
- Change from baseline in the derived ADCOMS score and change from baseline in imaging biomarkers (hippocampal, whole brain, and total ventricular volumes) at 12 and 18 months in MCI/Prodromal and mild AD subjects

*ApoE* status for heterozygous and homozygous E4 carriers will be included in the model to assess the effect of *ApoE* status in this relationship.

#### 9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

##### 9.7.1.7.1 PHARMACOKINETIC ANALYSES

The Safety Analysis Set will be used for individual E2609 concentration listings. The PK Analysis Set will be used for summaries of E2609 concentrations.

##### 9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Pharmacodynamic, PGx, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate statistical analysis plan. Please also refer to Appendix 3.

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). CSF Aβ(1-x), Aβ(1-42), t-tau, p-tau, and BACE1 will be assessed and data will be presented graphically. Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status.

Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels and exposure to E2609 in CSF will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. The PK/PD relationship between plasma PK parameters with other biomarkers may also be explored using similar methods.

Additionally, the relationship between plasma and CSF exposure to E2609 and the derived ADCOMS at 18 months, and the relationship between plasma and CSF exposure to E2609 and the change from baseline for 18 months in the ADAS-cog, the CDR, and the MMSE, will be explored graphically. Any emergent relationship will be explored through population PK/PD modeling.

Exposure-safety analyses may also be conducted.

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT2* phenotype of subjects enrolled in this study. The genomic DNA samples may also be stored and used as described in Section 9.7.1.7.2. Details of PGx testing may be provided and reported separately.

#### 9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, and vital sign measurements will be summarized by treatment group using descriptive statistics.

##### 9.7.1.8.1 Extent of Exposure

The extent of exposure to study drug will be summarized as cumulative extent of exposure in 3-month intervals. The number and percent of subjects will be presented by treatment group.

Duration of exposure will be summarized using descriptive statistics in 3-month intervals. The number and percent of subjects will be presented by treatment group.

#### 9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 17.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and preferred term. A subject will be counted only once within an SOC and preferred term, even if the subject experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and preferred term. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

Adverse events will be summarized by the following subgroups: *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI/Prodromal or mild AD).

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

#### 9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

Lymphocyte subsets (ie, CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages]) and regulatory T cells will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose.

Serum IgG, IgM, and IgA will be measured and summarized in the same manner as other laboratory parameters.

#### 9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

#### 9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to the end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 msec
- QTc interval >480 msec
- QTc interval >500 msec

Change from baseline in QTc interval:

- QTc interval increases from baseline >30 msec
- QTc interval increases from baseline >60 msec

#### 9.7.1.8.6 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-$cog_{14}$, MMSE, CDR, and CBB (see Section 9.7.1.6).

### 9.7.2 Determination of Sample Size

#### 9.7.2.1 Sample Size Rationale in the MCI/Prodromal Cohort

Primary endpoint – derived ADCOMS

The sample size and design characteristics to test the hypothesis for the primary objective based on the primary endpoint, change from baseline of the derived ADCOMS at 18 months, were determined by means of simulations. Extensive study simulations have shown that a total of 500 subjects will be sufficient to demonstrate that the most likely $ED_{90}$ dose achieves a 25% improvement over placebo with a probability of at least 80% in the interim and final analyses. There is at least a 90% probability of study success for the dose response scenarios

where treatment was considered to have a clinically meaningful treatment effect. Simulations have also shown that if there is no obvious dose effect, the probability of falsely claiming superiority to placebo is at most 5%.

For each of the 4 treatment groups (3 active doses and placebo) the final number of subjects per group will differ depending on the observed interim treatment responses. The simulation plan will be an appendix to the statistical analysis plan and will present further details.

vMRI

The null hypothesis is that there is no difference between active dose and placebo. There are 3 null hypotheses corresponding to 3 active doses. The alternative hypothesis is that at least 1 null hypothesis is false (1-sided). The null hypotheses will be tested using Dunnett's method with 1-sided alpha of 0.05. The statistical power was estimated through simulation for a moderate dose-response assumption that the percent reduction in change from baseline of total hippocampal volume compared with placebo would be 15%, 20%, and 25% corresponding to the 3 doses, respectively. The estimated power for the actual planned study sample size is 78% at 18 months assuming an attrition rate of 20% at 18 months. Under a stronger dose-response assumption (ie, the percent reduction in change from baseline of total hippocampal volume compared with placebo is twice as much as that in the moderate dose-response assumption), the estimated power is at least 99% at 18 months.

Amyloid PET

The null and alternative hypotheses and the statistical test are the same as those for vMRI. To estimate the sample size for the amyloid PET imaging subgroup at 18 months, a common SD of the change from baseline was estimated at 0.33 and a reasonable mean difference between treatment and placebo was estimated as 0.25 (standardized uptake value ratio [SUVR]). Assuming a moderate dose-response, the best dose would achieve a difference of 0.25 (SUVR) and the middle and low doses would achieve a difference of 0.2 and 0.15 (SUVR), respectively; this would require a total of 100 subjects from all 4 arms at 18 months to achieve 80% power.

#### 9.7.2.2 Sample Size Rationale for the Mild AD Cohort

ADCOMS at Month 18

The null hypothesis is that there is no difference between active dose and placebo. There are 2 null hypotheses corresponding to 2 active doses. The alternative hypothesis is that at least 1 null hypothesis is false. The null hypotheses will be tested using Dunnett's test with 2-sided alpha of 0.05 as described for the mild AD cohort in Section 9.7.1.6.2. The statistical power was estimated through simulation for the dose-response assumption that the percent reduction in change from baseline of ADCOMS at 18 months compared with placebo would be 33% and 50% corresponding to the 2 doses, respectively. The estimated power for the actual planned 200 mild AD subjects is at least 80% assuming a 2-sided alpha of 0.05.

### 9.7.3 Interim Analysis

***The MCI/Prodromal Cohort***

The Bayesian interim analyses and response adaptive randomization will be conducted by an unblinded external independent analysis group in accordance with the protocol. Oversight of the Bayesian interim analyses and response adaptive randomization will be conducted by an independent unblinded committee that has expertise with Bayesian adaptive design in clinical studies to ensure that the response adaptive randomization process and interim analyses perform as expected. The analysis group will provide the interim analysis outcomes to the committee at each interim analysis. The committee will ensure the integrity of the interim analysis and response adaptive randomization process through review of efficacy data. In addition, the committee will act in an independent advisory capacity to monitor the Bayesian interim analysis outcomes according to the early success and futility boundaries prespecified in the protocol. The committee will not be charged with any subject safety issues; this will remain the responsibility of the DSMB.

If the predefined early success criteria are met during the recruitment period, further recruitment and enrollment of MCI/Prodromal subjects into the study will stop (following confirmation from the Sponsor's Senior Management) and all currently randomized subjects will complete the full 18 months of treatment. No further interim analyses will be conducted after achieving early success.

If the predefined threshold for futility is reached, no additional subjects will be randomized into the study and the treatment of subjects already randomized into the study will stop and the study will be declared as "failed". All subjects will be monitored for safety for 3 months following their last dose.

If neither early success nor futility is reached and the study reaches full randomization, all subjects will complete 18 months of treatment. Interim efficacy analyses will be conducted every 3 months after full randomization is reached to assess futility and early success until all subjects complete 18 months of treatment. After full randomization, all study subjects will stop treatment only in the event of futility.

The DSMB will continue to monitor the safety aspects of the study throughout Stage A and Stage B. Details will be provided in the DSMB Charter. The study may be stopped for safety at any time.

An interim analysis will be conducted for safety when the first 60 MCI/Prodromal subjects have completed 12 weeks of treatment (or discontinue study drug early).

The first Bayesian adaptive interim analysis will be conducted when 100 MCI/Prodromal subjects have been randomized into the study (ie, 60 subjects from Stage A of the study and the first 40 subjects from Stage B of the study). Further interim efficacy analyses will be conducted after each additional 50 MCI/Prodromal subjects have been randomized, to a maximum of 500 MCI/Prodromal subjects (ie, at 100, 150, 200, 250, 300, 350, 400, 450,

500 subjects randomized). If the study reaches full randomization, additional interim analyses will be conducted every 3 months until all subjects complete 18 months of treatment. The study will be monitored for futility at each interim analysis. Starting at the interim analysis for 200 subjects, the study will be monitored for success at each interim analysis. Each interim analysis will be conducted on data for the derived ADCOMS.

In addition, at each interim efficacy analysis, response adaptive randomization will be used to update the allocation of new subjects between placebo and active doses according to a predefined automated algorithm.

***The Mild AD Cohort***

A group sequential design will be used for the mild AD cohort. This design includes 3 looks, 2 interim looks (when 60% and 80% information fractions are achieved) and 1 final look. The information fraction is the number of assessments in all treatment arms divided by the total number of expected assessments. Interim analyses will be performed after the MCI/Prodromal cohort crosses the early success boundary. The corresponding efficacy boundaries will be 0.076, 0.022, and 0.0423 for the first, second, and final analyses, respectively. If the actual information fraction during the interim analyses is different from 60% or 80% at the interim, the efficacy boundaries will be adjusted based on the actual information fraction.

If early success in the MCI/Prodromal cohort is not achieved before the final analysis that is performed when all subjects have completed 18 months treatment, then only a final analysis will be performed in mild AD subjects. In the event of futility in the MCI/Prodromal cohort, an analysis will be performed for the mild AD cohort based on the data for mild AD subjects available at that time.

Randomization into the Mild AD cohort will remain at a fixed schedule throughout Stage B of the study.

The interim analyses in the Mild AD cohort will be conducted by an independent analysis group.

### 9.7.4 Other Statistical/Analytical Issues

**Adaptive Randomization in the MCI/Prodromal Cohort**

Randomization to placebo or 1 of 3 dose groups of E2609 will be fixed for the first 100 subjects randomized in the study (1:1:1:1; placebo to each of the 3 active doses). Randomization probabilities to each treatment group will be updated at each interim analysis, such that the randomization probability will be increased for the placebo group and dosage groups that represent the potential target dose ($ED_{90}$), and simultaneously decreased for other active arms.

Within the 2 clinical populations (MCI/Prodromal and mild AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no).

Subjects with mild AD will be randomized to placebo or 1 of 2 dose groups of E2609.

### 9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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# 11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

## 11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

## 11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

## 11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

## 11.4 Recording of Data

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document, except when a section of the eCRF itself is used as the source document. Any correction to entries made on the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each eCRF. The investigator will report the eCRFs to the sponsor and retain a copy of the eCRFs.

## 11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents.

## 11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

## 11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

## 11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

## 11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

## 11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or CTA executed between the institution/investigator and the sponsor/CRO.

## 11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

## 11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

# 12 APPENDICES

## Appendix 1 Sponsor's Grading for Laboratory Values

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **BLOOD/BONE MARROW** | | | | |
| Hemoglobin (conversion from g/dL×0.6206) | **Female** (ULN=15.9 g/dL)<br><11.1 – 10.0 g/dL<br><111 – 100 g/L<br><6.9 – 6.2 mmol/L<br>**Male** (ULN=17.7 g/dL)<br><12.6 – 10.0 g/dL<br><126 – 100 g/L<br><7.8 – 6.2 mmol/L | <10.0 – 8.0 g/dL<br><100 – 80 g/L<br><6.2 – 4.9 mmol/L | <8.0 g/dL<br><80 g/L<br><4.9 mmol/L;<br>transfusion indicated | life-threatening consequences; urgent intervention indicated |
| Leukocytes (total white blood cell) | <3.40 – 3.0×$10^9$/L<br><3.40 $10^3$/uL – 3000/$mm^3$<br>(ULN=10.80 $10^3$/µL) | <3.0 – 2.0×$10^9$/L<br><3000 – 2000/$mm^3$ | <2.0 – 1.0×$10^9$/L<br><2000 – 1000/$mm^3$ | <1.0×$10^9$/L<br><1000/$mm^3$ |
| Lymphocytes | < 0.70 $10^3$/uL – 800/$mm^3$<br><0.70 – 0.8×$10^9$/L<br>(ULN=3.10 $10^3$/µL) | <800 – 500/$mm^3$<br><0.8 – 0.5×$10^9$/L | <500 – 200/$mm^3$<br><0.5 – 0.2×$10^9$/L | <200/$mm^3$<br><0.2×$10^9$/L |
| Neutrophils | <1.40– 1.5×$10^9$/L<br><1.40 $10^3$/uL – 1500/$mm^3$<br>(ULN=7.00 $10^3$/µL) | <1.5 – 1.0×$10^9$/L<br><1500 – 1000/$mm^3$ | <1.0 – 0.5×$10^9$/L<br><1000 – 500/$mm^3$ | <0.5×$10^9$/L<br><500/$mm^3$ |
| Platelets | <155 – 75.0×$10^9$/L<br><155 $10^3$/uL – 75,000/$mm^3$<br>(ULN=379 $10^3$/µL) | <75.0 – 50.0×$10^9$/L<br><75,000 – 50,000/$mm^3$ | <50.0 – 25.0×$10^9$/L<br><50,000 – 25,000/$mm^3$ | <25.0×$10^9$/L<br><25,000/$mm^3$ |
| **METABOLIC/LABORATORY** | | | | |
| Albumin, serum- low (hypoalbuminemia) | **2 - 59 years** (ULN=5.5 g/dL)<br><3.5 – 3 g/dL<br><35 – 30 g/L<br>**59 -69 years** (LLN-ULN)<br>3.6 g/dL – 4.8 g/dL<br>**69 -79 years** (LLN-ULN)<br>3.5g/dL – 4.8g/dL<br>**79 -89 years** (LLN-ULN)<br>3.5g/dL – 4.7g/dL<br>**89 -150 years** (LLN-ULN)<br>3.2g/dL – 4.6g/dL | <3 – 2 g/dL<br><30 – 20 g/L | <2 g/dL<br><20 g/L | life-threatening consequences; urgent intervention indicated |
| Alkaline phosphatase | **Female:**<br>**18 -19 years**<br>>101 – 3.0×101<br>**19 -61 years**<br>ULN=107<br>**61 -71 years**<br>ULN=112<br>**71 -150 years**<br>ULN=108<br>**Male**<br>**18 -19 years**<br>>127 – 3.0×127<br>**19 -61 years**<br>ULN=102<br>**61 -71 years**<br>ULN=103<br>**71 -150 years**<br>ULN=105 | >3.0 – 5.0×ULN<br>See previous column for ULN values | >5.0 – 20.0×ULN<br>See previous column for ULN values | >20.0×ULN<br>See previous column for ULN values |
| Alanine aminotransferase | **Female:**<br>>32 – 3.0×32<br>**Male:**<br>>44 – 3.0 x 44 | **Female:**<br>>3.0 – 5.0×32<br>**Male**<br>>3.0 – 5.0×44 | **Female:**<br>>5.0 – 20.0×32<br>**Male:**<br>>5.0 – 20.0×44 | **Female:**<br>>20.0×32<br>**Male:**<br>>20.0×44 |
| Aspartate aminotransferase | >40 – 3.0×40 | >3.0 – 5.0×40 | >5.0 – 20.0×40 | >20.0×40 |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Bilirubin (hyperbilirubinemia) | >1.2 – 1.5×1.2 | >1.5 – 3.0×1.2 | >3.0 – 10.0×1.2 | >10.0×1.2 |
| Calcium, serum-low (hypocalcemia) (conversion to mmol×0.25) | <8.5 – 8.0 mg/dL<br><2.13 – 2.0 mmol/L | <8.0 – 7.0 mg/dL<br><2.0 – 1.75 mmol/L | <7.0 – 6.0 mg/dL<br><1.75 – 1.5 mmol/L | <6.0 mg/dL<br><1.5 mmol/L |
| Calcium, serum-high (hypercalcemia) | >10.6 – 11.5 mg/dL<br>>2.65 – 2.9 mmol/L | >11.5 – 12.5 mg/dL<br>>2.9 – 3.1 mmol/L | >12.5 – 13.5 mg/dL<br>>3.1 – 3.4 mmol/L | >13.5 mg/dL<br>>3.4 mmol/L |
| Cholesterol, serum-high (hypercholesterolemia) (conversion to mmol/L ×0.02586) | **0 -19 years**<br>>169 – 300 mg/dL<br>>4.37 – 7.75 mmol/L<br>**19 -150 years**<br>>199 – 300 mg/dL<br>>5.15 – 7.75 mmol/L | >300 – 400 mg/dL<br>>7.75 – 10.34 mmol/L | >400 – 500 mg/dL<br>>10.34 – 12.92 mmol/L | >500 mg/dL<br>>12.92 mmol/L |
| Creatinine | **Female**<br>>1.00 mg/dL – 1.5×1.00<br>**Male**<br>>1.27 mg/dL – 1.5×1.27 | **Female**<br>>1.5 – 3.0×1.00<br>**Male**<br>>1.5 mg/dL – 3.0×1.27 | **Female**<br>>3.0 – 6.0×1.00<br>**Male**<br>>1.5 mg/dL – 3.0×1.27 | **Female**<br>>6.0×1.00<br>**Male**<br>>1.5 mg/dL-3.0×1.27 |
| Gamma glutamyl transpeptidase | **Female**<br>>60 IU/L – 3.0×60<br>**Male**<br>>65 IU/L – 3.0×65 | **Female**<br>>3.0 – 5.0×60<br>**Male**<br>>3.0 – 5.0×65 | **Female**<br>>5.0 – 20.0×60<br>**Male**<br>>5.0 – 20.0×65 | **Female**<br>>20.0×60<br>**Male**<br>>20.0×65 |
| Glucose, serum-high (hyperglycemia) (conversion to mmol/L ×0.0555) | **Fasting glucose value**<br>>99 – 160 mg/dL<br>>5.5 – 8.9 mmol/L | **Fasting glucose value**<br>>160 – 250 mg/dL<br>>8.9 – 13.9 mmol/L | >250 – 500 mg/dL;<br>>13.9 – 27.8 mmol/L;<br>hospitalization indicated | >500 mg/dL;<br>>27.8 mmol/L;<br>life-threatening consequences |
| Glucose, serum-low (hypoglycemia) | <65 – 55 mg/dL<br><3.6 – 3.0 mmol/L | <55 – 40 mg/dL<br><3.0 – 2.2 mmol/L | <40 – 30 mg/dL<br><2.2 – 1.7 mmol/L | <30 mg/dL<br><1.7 mmol/L<br>life-threatening consequences;<br>seizures |
| Phosphate, serum-low (hypophosphatemia) (conversion to mmol/L ×0.323) | <2.5 – 2.5 mg/dL<br><0.81 – 0.8 mmol/L | <2.5 – 2.0 mg/dL<br><0.8 – 0.6 mmol/L | <2.0 – 1.0 mg/dL<br><0.6 – 0.3 mmol/L | <1.0 mg/dL<br><0.3 mmol/L<br>life-threatening consequences |
| Potassium, serum-high (hyperkalemia) | >5.5 – 5.5 mmol/L | >5.5 – 6.0 mmol/L | >6.0 – 7.0 mmol/L<br>hospitalization indicated | >7.0 mmol/L<br>life-threatening consequences |
| Potassium, serum-low (hypokalemia) | <3.5 mEq/L – 3.0 mmol/L | <LLN – 3.0 mmol/L;<br>symptomatic; intervention indicated | <3.0 – 2.5 mmol/L<br>hospitalization indicated | <2.5 mmol/L<br>life-threatening consequences |
| Sodium, serum-high (hypernatremia) | >144 mEq/L – 150 mmol/L | >150 – 155 mmol/L | >155 – 160 mmol/L<br>hospitalization indicated | >160 mmol/L<br>life-threatening consequences |
| Sodium, serum-low (hyponatremia) | <134 mEq/L – 130 mmol/L | Not applicable | <130 – 120 mmol/L | <120 mmol/L<br>life-threatening consequences |
| Triglyceride, serum-high (hypertriglyceridemia) | 150 – 300 mg/dL<br>1.71 – 3.42 mmol/L | >300 – 500 mg/dL<br>>3.42 – 5.7 mmol/L | >500 – 1000 mg/dL<br>>5.7 – 11.4 mmol/L | >1000 mg/dL<br>>11.4 mmol/L<br>life-threatening consequences |
| Uric acid, serum-high (hyperuricemia) | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | Not applicable | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | >10 mg/dL<br>>0.59 mmol/L<br>life-threatening consequences |

LLN = lower limit of normal, ULN = upper limit of normal.

# Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, Listing 3, Listing 4, Listing 5, and Listing 6. Medications permitted with restrictions are listed in Listing 7, Listing 8, and Listing 9. **These may not be all-inclusive listings.** Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-202 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 9 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

## Prohibited Prior/Concomitant Medications

### Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Prohibited from 14 days (or 5 half-lives, whichever is longer) before Randomization until after the last treatment visit** | | |
| **Anti-arrhythmic/ abnormal heart rhythm** | | |
| Amiodarone | Cordarone; Pacerone | Incidence in females greater than males, Torsades de Pointes risk regarded as low |
| Disopyramide | Norpace | Incidence in females greater than males |
| Dofetillide | Tikosyn | |
| Ibutilide | Corvert | Incidence in females greater than males |
| Procainamide | Pronestyl; Procan | |
| Quinidine | Cardioquin; Quinaglute | Incidence in females greater than males |
| Sotalol | Betapace | Incidence in females greater than males |
| **Antihistamine/ allergic rhinitis** | | |
| Astemizole | Hismanal | No longer available in United States |
| Terfenadine | Seldane | No longer available in United States |
| **Anti-anginal/ heart pain** | | |
| Bepridil | Vascor | Incidence in females greater than males |
| **Antibiotic/ bacterial infection** | | |
| Clarithromycin | Blaxin | |
| Moxifloxacin | Avelox | |
| Sparfloxadin | Zagam | |
| **Listing 1 continued** | | |
| **Antimalarial/ malaria infection** | | |
| Chloroquine | Aralen | |
| Halofantrine | Halfan | Incidence in females greater than males |
| **Antipsychotic/ anti-emetic/ schizophrenia/ nausea** | | |
| Chloropromazine | Thorazine | |
| **Gastrointestinal stimulant/ heartburn** | | |
| Cisapride | Propulsid | |

## Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Antinausea/ nausea** | | |
| Domperidone | Motillum | Not available in the United States |
| **Sedative; antinausea/ anesthesia adjunct, nausea** | | |
| Droperidol | Inapsine | |
| **Antibiotic; gastrointestinal stimulant/ bacterial infection; increase gastrointestinal motility** | | |
| Erythromycin | Erythrocin; E.E.S. | Incidence in females greater than males |
| **Antipsychotic/ schizophrenia** | | |
| Haloperidol | Haldol | When given intravenously or at higher than recommended doses, risk of sudden death, QT prolongation, and torsades increases |
| Mesoridazine | Serentil | |
| Thioridazine | Mellaril | |
| **Opiate agonist/ pain control, narcotic dependence** | | |
| Levomethadyl | Orlaam | |
| Methadone | Methadose; Dolophine | Incidence in females greater than males |
| **Anti-infective/ pneumocystis pneumonia** | | |
| Pentamidine | Pentam; NebuPent | Incidence in females greater than males |
| **Antipsychotic/ Tourette's tics** | | |
| Pimozide | Orap | Incidence in females greater than males |
| **Antilipemic/ hypercholesterolemia** | | |
| Probucol | Lorelco | No longer available in United States |
| **Anticancer** | | |
| Arsenic trioxide | Trisenox | Used for leukemia |
| Vandetanib | Zactima | Used for thyroid cancer |

Note: This list is not exhaustive.
QTc = Corrected QT interval.

## Listing 2 Prohibited Medications Within 7 Days (or 5 Half-lives, Whichever is Longer) Before Randomization and Until after the Last Treatment Visit)

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Anticoagulants** | |
| Adeporin | Normiflo |
| Alteplase, tPA | Activase, Cathflo Activase |
| Anisindione | Miradon |
| Antithrombin III | ATryn, Thrombate III |
| Argatroban | Argatroban |
| Bivalirudin | Angiomax |
| Dabigatran | Pradaxa |
| Dalteparin | Fragmin |
| Danaparoid | Orgaran |
| Dicumarol | Dicumarol |
| Enoxaparin | Lovenox |
| Fondaparinux | Arixtra |
| Heparin Sodium | Monoject |
| Lanoteplase | Lanoplase |
| Lepirudin | Refludan |
| Pentosan polysulfate sodium | Elmiron |
| Reteplase | Retavase, Retevase |
| Staphylokinase | Eskinase, Heberkinasa Kabikinase, Streptase, Thrombosolv, Zykinase |
| Streptokinase | Streptase |
| Tenecteplase | TNKase |
| Tinzaparin | Innohep |
| Urokinase | Abbokinase, Kinlytic |
| Warfarin | Coumadin, Jantoven |
| **Antiplatelet drugs** | |
| Aspirin and Plavix (only in subjects undertaking lumbar puncture in biomarker subgroup) | Aspirin or clopidogrel is permitted in all subjects. Aspirin and clopidogrel in combination is permitted in subjects who are not to undergo lumbar puncture. |

Note: This list is not exhaustive.

## Listing 3 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Randomization and Until after the Last Treatment Visit

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Systemic Immunosuppressants[a] and Immunomodulatory therapy** | |
| Azathioprine | Azasan, Imur |
| Ciclosporine | Gengraf, Neoral |
| Dexamethasone | Decadron, Dexasone, Diodex, Hexadrol, Maxidex |
| Fingolimod | Gilenya |
| Methotrexate | Trexall |
| Methylprednisolone | Medrol, Meprolone |
| Mycophenolate | CellCept, Myfortic |
| Prednisolone | Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS |

Note: This list is not exhaustive.

a: Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

## Listing 4 Prohibited Medications Within 6 Months Before Randomization

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Immunoglobulin therapy** | |
| Adalimumab | Humira |
| Bevacizumab | Avastin |
| Efalizumab | Raptiva |
| Etanercept | Enbrel |
| Immune globulin IV, IVIG, IGIV | Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S |
| Infliximab | Remicade |
| Omalizumab | Xolair |
| Ranibizumab | Lucentis |
| Other monoclonal antibodies not listed here | |

Note: This list is not exhaustive.

### Listing 5 Prohibited Live Vaccines Within 3 Months Before Randomization Until after the Last Treatment Visit (this does not apply to non-live/inactivated vaccines)

| **Bacterial vaccines** | **Viral vaccines** |
|---|---|
| Bacillus Calmette-Guérin vaccine against tuberculosis | Measles vaccination |
| Cholera vaccination (oral) | Rubella vaccination |
| | Oral polio vaccination (Sabin) |
| | Yellow fever vaccination |
| | Varicella (chickenpox) vaccination |
| | Rotavirus vaccination |
| | Japanese encephalitis vaccination |
| | Live attenuated influenza vaccine (FluMist, Fluenz) |
| Typhoid vaccination (oral) | Mumps vaccination |

Note: This list is not exhaustive

## Listing 6 Strong CYP3A4 Inhibitors Prohibited Within 5 Half-Lives or 14 Days (Whichever Is Longer) Before Randomization Until After the Last Treatment Visit

| Generic name | Brand name(s) |
|---|---|
| boceprevir | Victrelis |
| clarithromycin | Clarithromycin, clarithromycin extended release, Prevpac |
| cobicistat | Tybost, Stribild, |
| conivaptan | Vaprisol |
| danoprevir | |
| elvitegravir | Vitekta, Stribild |
| indinavir | Crixivan |
| itraconazole | Sporanoz, Onmel |
| ketoconazole | Xolegel, Nizoral, Ketodan |
| lopinavir | Kaletra |
| nefazodone | Serzone |
| nelfinavir | Viracept |
| posaconazole | Noxafil |
| ritonavir | Norvir, Kaletra |
| saquinavir | Invirase, Fortovase |
| telaprevir | Incivek |
| telithromycin | Ketek |
| tipranavir | Aptivus |
| troleandomycin | Triocetin |
| voriconazole | Vfend, Voriconazole |

Note: This list is not exhaustive

## Permitted Prior/Concomitant Medications

### Listing 7 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Baseline Cognitive Assessments at Visit 2 and Remain on the Same Stable Dose from Baseline to Follow-Up Visit 2

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Cognitive Enhancers** | |
| Donepezil | Aricept |
| Galantamine | Reminyl |
| Memantine | Namenda |
| Rivastigmine | Exelon |

Note: This list is not exhaustive.

## Listing 8 Permitted Medications Used on PRN Basis Which are Not to be Used Within 72 Hours before Cognitive Testing

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Opiates** | |
| Morphine | Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol |
| **Opiate Agonists** | |
| Codeine | Codeine |
| Fentanyl | Actiq, Duragesic, Fentora, Onsolis, Sublimaze |
| Meperidine | Demerol, Meperitab |
| Oxycodone | Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol |
| Other opioids or opioid agonists which are used on PRN basis | |
| **Benzodiazepines and sedatives** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Amitriptyline | (various) |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Dothiepin | (various) |
| Estazolam | ProSom |
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |
| Lorazepam | Ativan |
| Midazolam | Versed |
| Olanzapine | Zyprexa |
| Promethazine | Phenergan; others |
| Ramelteon | Rozerem |
| Risperidone | Risperdal |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zolpidem | Ambien; others |
| Zopiclone | (various) |
| Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives | |

Note: This list is not exhaustive

PRN = Pro re nata

## Listing 9 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| If to be used on a PRN basis see Listing 8. If to be used chronically, subjects must be on a stable dose for ≥4 weeks before Baseline. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks. | |
| **Antidepressants** | |
| Amitriptyline hydrochloride | Elavil |
| Amoxapine | Amoxapine |
| Bupropion | Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin |
| Citalopram | Celexa |
| Clomipramine hydrochloride | Anafranil |
| Desipramine hydrochloride | Norpramin |
| Desvenlafaxine | Pristiq |
| Doxepin hydrochloride | Prudoxin, Silenor, Sinequan, Zonalon |
| Duloxetine | Cymbalta |
| Escitalopram | Lexapro |
| Fluoxetine | Prozac, Sarafem, Selfemra |
| Fluvoxamine | Luvox |
| Imipramine hydrochloride | Tofranil |
| Isocarboxazid | Marplan |
| Maprotiline hydrochloride | Ludiomil |
| Mirtazapine | Remeron Soltab |
| Nortriptyline hydrochloride | Aventyl, Pamelor |
| Paroxetine | Paxil, Pexeva |
| Phenelzine | Nardil |
| Protriptyline hydrochloride | Vivactil |
| Rasagiline | Azilect |
| Selegiline | EMSAM |
| Sertraline | Sertaraline, Zoloft |
| Tranylcypromine | Parnate |
| Trazodone hydrochloride | Desyrel, Oleptro |
| Trimipramine maleate | Surmontil |
| Venlafaxine hydrochloride | Effexor |

## Listing 9 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Mood Stabilizers (Listing 8 continued)** | |
| Carbamazepine | Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR |
| Lamotrigine | Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR |
| Valproic acid | Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate |
| **Antipsychotics** | |
| Acetophenazine | Tindal |
| Aripiprazole | Abilify |
| Asenapine | Saphris |
| Olanzapine | Zyprexa |
| Chlorpromazine | Thorazine |
| Haloperidol | Haloperidol, Haldol |
| Clozapine | Clozaril, Fazaclo |
| Fluphenazine | Prolixin |
| L-Methylfolate | Deplin, L-Methylfolate Calcium |
| Loxapine | Loxitane |
| Mesoridazine | Serentil |
| Perphenazine | Trilafon |
| Quetiapine | Seroquel |
| Risperidone | Risperdal |
| Thioridazine | Mellaril |
| Thiothixene | Navane |
| Trifluoperazine | Stelazine |
| **Benzodiazepines** | |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Chlordiazepoxide | H-Tran, Librium |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Estazolam | ProSom |
| Flunitrazepam | Rohypnol |
| Flurazepam | Dalmane |

## Listing 9 Permitted Centrally Active or Psychiatric Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| Lorazepam | Ativan |
| Midazolam | Versed |
| Temazepam | Restoril |
| Triazolam | Halcion |
| Zopiclone | Imovane, Zimovane |
| Zopidem | Ambien, Ambien CR, Intermezzo, Stilnox, Stilnoct, Sublinox, Hypnogen, Zolsana |

Note: This list is not exhaustive.

PRN = Pro re nata

# Appendix 3 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

## Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

## Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

### Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

### Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not

currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

# Appendix 4 AEs Indicating Signals of Possible Drug Abuse Potential

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| 1 | **Euphoric mood** | Euphoric mood |
| | | Euphoria |
| | | Euphoric |
| | | Exaggerated well-being |
| | | Excitement excessive |
| | | Feeling high |
| | | Felt high |
| | | High |
| | | High feeling |
| | | Laughter |
| 2 | **Elevated mood** | Elevated mood |
| | | Mood elevated |
| | | Elation |
| 3 | **Feeling abnormal** | Feeling abnormal |
| | | Cotton wool in head |
| | | Feeling dazed |
| | | Feeling floating |
| | | Feeling strange |
| | | Feeling weightless |
| | | Felt like a zombie |
| | | Floating feeling |
| | | Foggy feeling in head |
| | | Funny episode |
| | | Fuzzy |
| | | Fuzzy head |
| | | Muzzy head |
| | | Spaced out |
| | | Unstable feeling |
| | | Weird feeling |
| | | Spacey |
| 4 | **Feeling drunk** | Feeling drunk |
| | | Drunkenness feeling of |
| | | Drunk-like effect |
| | | Intoxicated |
| | | Stoned |
| | | Drugged |
| 5 | **Feeling of relaxation** | Feeling of relaxation |
| | | Feeling relaxed |
| | | Relaxation |
| | | Relaxed |
| | | Increased well-being |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Excessive happiness |
| 6 | **Thinking abnormal** | Thinking abnormal |
| | | Abnormal thinking |
| | | Thinking irrational |
| | | Thinking disturbance |
| | | Thought blocking |
| | | Wandering thoughts |
| 7 | **Hallucination** | Hallucination |
| | | Illusions |
| | | Flashbacks |
| | | Floating |
| | | Rush |
| | | Feeling addicted |
| 8 | **Inappropriate affect** | Elation inappropriate |
| | | Exhilaration inappropriate |
| | | Feeling happy inappropriately |
| | | Inappropriate affect |
| | | Inappropriate elation |
| | | Inappropriate laughter |
| | | Inappropriate mood elevation |
| 9 | **Mood disorders and disturbances** | Mental disturbance |
| | | Depersonalisation |
| | | Psychomotor stimulation |
| | | Mood disorders |
| | | Emotional and mood disturbances |
| | | Delirium |
| | | Delirious |
| | | Mood altered |
| | | Mood alterations |
| | | Mood instability |
| | | Mood swings |
| | | Emotional lability |
| | | Emotional disorder |
| | | Emotional distress |
| | | Personality disorder |
| | | Impatience |
| | | Abnormal behavior |
| | | Delusional disorder |
| | | Irritability |
| 10 | **Drug tolerance** | Drug tolerance |
| | | Habituation |
| | | Drug withdrawal syndrome |
| | | Substance-related disorders |
| 11 | **Psychosis** | Psychosis |

| | Category | Examples of AEs Indicating Signals of Possible Drug Abuse Potential |
|---|---|---|
| | | Psychotic episode or disorder |
| 12 | **Dissociative State** | Dissociation |
| | | Disconnected |
| | | Derealisation |
| | | Depersonalisation |
| | | Detached |
| | | Sensation of distance from one's environment |
| | | Loss of a sense of personal identity |

# PROTOCOL SIGNATURE PAGE

**Study Protocol Number:** E2609-G000-202
**Study Protocol Title:** A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability and Efficacy of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's Disease
**Investigational Product Name:** E2609
**IND Number:** 109308
**EudraCT Number:** 2014-002723-94

**SIGNATURES**
Authors:

PPD Date

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Eisai Ltd.

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Neuroscience and General Medicine Product Creation Unit
Eisai Inc.

# INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof-of-Concept, Dose-Finding Study To Evaluate Safety, Tolerability and Efficacy of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's Disease |
| **Investigational Product Name:** | E2609 |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

| Investigator | Signature | Date |
|---|---|---|

# 1 TITLE PAGE


## Clinical Study Protocol

| | |
|---|---|
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| **Sponsor:** | Eisai Inc.<br>155 Tice Boulevard<br>Woodcliff Lake,<br>New Jersey 07677<br>United States<br><br>Eisai Ltd.<br>European Knowledge Centre<br>Mosquito Way<br>Hatfield,<br>Hertfordshire<br>AL10 9SN<br>United Kingdom<br><br>Eisai Co., Ltd.<br>4-6-10 Koishikawa<br>Bunkyo-Ku,<br>Tokyo 112 8088<br>Japan |
| **Investigational Product Name:** | E2609 |
| **Indication:** | Alzheimer's disease |
| **Phase:** | 2 |
| **Approval Date:** | V1.0 15 July 2014 (original protocol) |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |
| **GCP Statement:** | This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities. |
| **Confidentiality Statement:** | This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study. |

# 2 CLINICAL PROTOCOL SYNOPSIS

**Compound No.:**
E2609

**Name of Active Ingredient:**
*N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

**Study Protocol Title**
A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof of Concept, Dose-Finding Study To Evaluate Safety, Tolerability and Efficacy of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's Disease

**Investigators**
Stage A: Investigators in United States only

Stage B: Multinational investigators

**Sites**
Stage A: Approximately 25 sites, United States only

Stage B: Approximately 125 sites, globally

**Study Period and Phase of Development**
Stage A: Approximately 32 months and will continue and overlap with Stage B

Stage B: A maximum of 40 months from initiation of Stage B

Phase 2

**Objectives**

**Primary Objectives**

1. To evaluate the efficacy of daily dosing with 3 doses of E2609 compared with placebo by establishing the lowest effective dose that achieves 90% of the greatest treatment effect ($ED_{90}$) for E2609 on the derived Alzheimer's Disease Composite Score (ADCOMS) at 18 months of treatment in subjects with Mild Cognitive Impairment due to Alzheimer's Disease/ Prodromal Alzheimer's Disease (referred to as MCI/Prodromal throughout the protocol)
2. To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with Mild Dementia due to Alzheimer's Disease (referred to as mild AD throughout the protocol)

**Secondary Objectives**

1. To evaluate the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects, as measured by volumetric magnetic resonance imaging (vMRI)
2. To evaluate the effect of E2609 compared with placebo on amyloid β(1-x) (Aβ[1-x]) in cerebrospinal fluid (CSF) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
3. To evaluate the efficacy of E2609 compared with placebo on the derived ADCOMS at 18 months in mild AD subjects

**Exploratory Objectives**

1. To explore the effect of E2609 compared with placebo on the derived ADCOMS following 12 months of treatment in MCI/Prodromal and mild AD subjects
2. To explore the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in mild AD subjects, as measured by vMRI
3. To explore the effects of E2609 compared with placebo on Aβ(1-42) in CSF after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
4. To explore the effects of E2609 compared with placebo on Aβ(1-x) and Aβ (1-42) in CSF after 4 weeks and 18 months of treatment in mild AD subjects
5. To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during post treatment follow-up, in MCI/Prodromal and mild AD subjects, by assessment of:
   a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
   b. The Clinical Dementia Rating (CDR) scale
   c. The Mini-Mental State Examination (MMSE)
   d. The CogState Brief Battery (CBB)
   e. The Functional Assessment Questionnaire (FAQ; also known as the Functional Activities Questionnaire)
   f. The International Shopping List Task (ISLT)
6. To explore the effects of E2609 compared with placebo on various biomarkers in MCI/Prodromal and mild AD subjects. Biomarkers to be explored include:
   a. CSF biomarkers of neurodegeneration (eg, tau, phosphorylated-tau [p-tau]) after 18 months of treatment
   b. Plasma and CSF amyloid, and CSF β-amyloid converting enzyme 1 (BACE1) measurements during 18 months of treatment and during post treatment follow-up
   c. vMRI measurements including left and right hippocampal volume, whole brain volume and total ventricular volume at 6, 12, and 18 months of treatment and during post treatment follow-up
   d. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)

7. To characterize the population pharmacokinetics (PK) of E2609 in MCI/Prodromal and mild AD subjects, and to examine the effect of intrinsic and extrinsic factors (including N-acetyltransferase 2 [*NAT2*] phenotype) on the PK
8. To explore the relationship between the treatment effects of E2609 on the ADCOMS and its effects on CSF amyloid, CSF BACE1, CSF tau, and vMRI in MCI/Prodromal and mild AD subjects

**Study Design**

This will be a multicenter placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild AD. A common set of inclusion criteria, consistent with the National Institute on Aging – Alzheimer's Association (NIA-AA) clinical research criteria for Mild Cognitive Impairment (MCI) due to Alzheimer's Disease (AD) or mild AD, will be required for all subjects. In addition the MCI due to AD population will also qualify under the research criterion for "Prodromal AD." As the non-demented subjects will fulfill the criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria.

The study will be conducted in 2 stages, Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 (at least 12 weeks) in MCI/Prodromal subjects before expanding enrollment to include a larger population of MCI/Prodromal subjects in Stage B. In addition, during Stage B of the study, subjects with mild AD will be randomized to form a separate mild AD cohort. All MCI/Prodromal subjects will be included in the primary efficacy evaluation irrespective of whether they were recruited during Stage A or Stage B of the study. Bayesian adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B.

Both Stage A and Stage B of the study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days) includes a Screening Visit (Visit 1) and a Baseline Visit (Visit 2). All screening assessments (within 4 distinct tiers) must be completed, and eligibility to continue in the study confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

**Stage A**

Stage A will enroll 60 eligible MCI/Prodromal AD subjects who will be randomized (at Visit 3) 1:1:1:1 to 4 treatment groups. In addition to the placebo group, 3 E2609 doses will be used to reduce CSF amyloid β levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/pharmacodynamic (PD) modeling has shown that these doses should achieve these targets when administered once daily (QD) with food, and these doses will be confirmed or adjusted based on the 4-week assessment of CSF Aβ(1-x)

During Stage A, safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the first subject is randomized during Stage A of the study, an independent data safety monitoring board (DSMB; including at least 1 immunologist) will review all safety data in an unblinded manner. The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. Unless the DSMB recommends otherwise, randomization of subjects into Stage A of the study will continue until 60 MCI/Prodromal subjects have been randomized and dosed.

After 60 MCI/Prodromal subjects in Stage A have completed 4 weeks of treatment, an interim analysis of the E2609 PK and PD profiles will be used to confirm the E2609 doses to be used for Stage B. If the 95% confidence interval of the mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment with a dose of E2609 does not include its intended target value (ie, 25%, 50% and 75% reductions from baseline, respectively for E2609 at 5 mg, 15 mg, and 50 mg QD), PK/PD modeling will be conducted. From this model, the new target plasma steady state concentrations of E2609 required to achieve the target levels of CSF Aβ(1-x) reduction will be estimated again. Dose adjustment for Stage B may be considered if it is possible to get closer to the new target plasma steady state concentrations of E2609 required to achieve the intended target levels of CSF Aβ(1-x) reduction than is possible with the initially planned doses, given the limitation that E2609 dose adjustments will have to be in 5-mg increments or decrements. Subjects already randomized to a dose that needs to be adjusted will be switched to the new adjusted dose and complete their treatment at this new dose.

Once 60 MCI/Prodromal subjects in Stage A have completed at least 12 weeks of treatment, an interim safety analysis will be conducted by Eisai and the DSMB. Subjects in Stage A will continue study drug while the DSMB reviews all the available safety data, but randomization of additional subjects will not take place (ie, recruitment into Stage B will not commence) until the safety analysis is completed by the DSMB.

**Stage B**

Stage B will start after the DSMB safety review of Stage A has shown acceptable safety and tolerability of E2609 and after the doses of E2609 to be used in Stage B are confirmed. Stage B will enroll, randomize, and dose up to an additional 440 eligible MCI/Prodromal subjects. In addition, a separate cohort of approximately 200 mild AD subjects will be randomized and dosed during Stage B. Safety data from Stage B will continue to be reviewed by the DSMB (approximately every 3 months) until recruitment to the study is completed; following this the DSMB will meet approximately every 6 months.

Both population cohorts will include separate placebo groups. The MCI/Prodromal cohort will include 3 doses of E2609 (5 mg, 15 mg, and 50 mg QD) whereas the mild AD cohort will only include 2 doses of E2609 (15 mg and 50 mg QD).

Bayesian adaptive randomization will be used in the MCI/Prodromal cohort only during Stage B. The first 40 MCI/Prodromal subjects recruited into Stage B will be randomized according to a fixed schedule (1:1:1:1; placebo: 5 mg E2609: 15 mg E2609: 50 mg E2609)

and the remaining subjects in the MCI/Prodromal cohort in Stage B will be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. The mild AD subjects will be randomized according to a fixed schedule (1:1:1 placebo; 15 mg E2609; 50 mg E2609) throughout Stage B of the study.

**Early discontinuation**

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug. Subjects who discontinue study drug prematurely will also be scheduled to return to the study site to undertake limited efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, CBB, and ISLT) at Week 53 (Visit 16) and Week 79 (Visit 18), if these 2 visits have not already been performed.

**Follow up**

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug (Visit 19) and a second 12 weeks after the last dose of study drug (Visit 20). If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the posttreatment Follow-Up period.

**Number of Subjects**

- Stage A: Approximately 250 MCI/Prodromal subjects will be screened to provide 60 randomized subjects (target of 15 subjects per treatment arm).
- Stage B: Approximately 1850 MCI/Prodromal subjects will be screened to provide up to 440 enrolled subjects. The final number of MCI/Prodromal subjects will depend upon whether the prespecified criteria for either early success or futility are met. In addition, approximately 835 subjects with mild AD will be screened to provide approximately 200 randomized mild AD subjects.

**Inclusion Criteria**

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD or AD dementia and is "staged" or classified as either MCI (Stage A and Stage B) or mild dementia (Stage B only) and also complies with the following:

**Required at both Screening and Baseline:**

   a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician’s observation
   b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT
   c. FAQ ≤20
   d. MMSE ≥20

2. Amyloid positive PET image based on centralized PET scan reading
3. Males and females aged 50 to 85 years, inclusive at time of consent

4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.
5. Subjects who are receiving acetylcholinesterase inhibitors (AChEIs) or memantine must be on a stable dose for at least 12 weeks before the baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.
6. Subjects must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization.
7. Females must not be lactating or pregnant (as documented by a negative beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
8. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception other than hormonal contraceptives (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. If currently abstinent, the subject must agree to use a double barrier method as described above if she becomes sexually active during the study period or for 30 days after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for ≥12 consecutive months, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (ie bilateral tubal ligation, total hysterectomy or bilateral oophorectomy, all with surgery ≥1 month before dosing).

9. Male subjects must have had a successful vasectomy (confirmed azoospermia) or they and their female partners must meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period and for 30 days after study drug discontinuation). No sperm donation is allowed during the study period and for 30 days after study drug discontinuation.
10. Provide written informed consent
11. Willing and able to comply with all aspects of the protocol

**Exclusion Criteria**

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or magnetic resonance imaging (MRI)
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening
4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (eg, arachnoid cysts) or brain tumors (eg, meningioma).
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could confound the MCI/Prodromal or mild AD diagnosis or could interfere with study assessments or procedures
7. A score of ≥8 on the 15-item Geriatric Depression Scale at Screening
8. Abnormally low serum vitamin B12 levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the lower limit of normal (LLN) for the testing laboratory).
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
11. Any contraindications to lumbar puncture for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity)

12. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
13. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
14. Subjects with chronic viral hepatitis
15. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
16. A history of ophthalmic shingles
17. A history of ocular herpes simplex virus (HSV) infection
18. Any live vaccine in the 3 months before randomization
19. Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests conducted at Visit 2 (eg, MMSE, CDR, etc) must be repeated.
20. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
21. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below LLN and confirmed by a repeat test conducted 1 week after the initial test
22. Ig (IgG, IgA, or IgM) levels below the LLN
23. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
24. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate electrocardiograms (ECGs). A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
25. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
26. Left bundle branch block at Screening or Baseline
27. Persistent heart rate <50 or >100 beats per minute at Screening or Baseline
28. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening

29. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
30. Type 1 or Type 2 diabetes mellitus that is not well controlled
31. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.
32. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
33. Hypopigmentation conditions (eg, albinism and vitiligo)
34. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive for benzodiazepines or opioids in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications containing benzodiazepines or opioids for a medical condition that is not exclusionary and not due to drug abuse.
35. Has a "yes" answer to the Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
36. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
37. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
38. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
39. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
40. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation

**Study Treatments**

E2609 tablets of 5-mg, 10-mg and 25-mg dose strengths will be supplied. Placebo tablets to match E2609 will be of identical appearance. Each subject will receive 2 tablets, which when combined will make up the required doses of E2609 (see below) or placebo, to be administered orally QD with food.

- MCI/Prodromal Cohort: 3 doses (5 mg, 15 mg, and 50 mg) of E2609 or placebo
- Mild AD Cohort: 2 doses (15 mg and 50 mg) of E2609 or placebo.

**Duration of Treatment**

The maximum duration of a subject's participation in the study will be approximately 2 years, comprising:

- Screening and Baseline Periods (Prerandomization Phase): up to 60 days
  - In subjects who have an active infection within 4 weeks of the planned randomization date, the duration of the pre-randomization phase can be extended by up to 4 weeks to allow additional time for resolution of the infection.
- Treatment Period (Randomization Phase): up to 78 weeks
- Follow-Up Period (Randomization Phase): 12 weeks (post last dose)

**Concomitant Drug/Therapy**

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit:

- Anticoagulants (eg, warfarin, digabatrin) are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization
- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization

Subjects taking AChEIs or memantine must meet the following criteria in order to be included in the primary analyses:

- On a stable dose for 12 weeks before the baseline cognitive assessments at Visit 2
- Remain on a stable dose while on study

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the

study, but their clinical efficacy data will be censored from the time of drug initiation for the primary analyses.

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if, in the opinion of the investigator, this will not interfere with study procedures or subject safety, and are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks.

**Assessments**

**Efficacy Assessments**

Derived ADCOMS: The derived ADCOMS represents a new approach to the analysis of selected items (12 total) from 3 fully validated and well established clinical tools, the ADAS-cog (4 items), the MMSE (2 items), and the CDR (all 6 items). The 3 scales should be administered in full in the morning, or, if not possible, consistently at the same time of day.

Alzheimer's Disease Assessment Scale - cognitive subscale: The 14-item version will be used since it is considered more relevant for subjects with MCI/Prodromal AD or mild AD.

Mini Mental State Examination: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing.

Clinical Dementia Rating: Assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

CogState Brief Battery: A computer-based battery comprising 4 cognitive tests:

1. Detection – a simple reaction time test. Speed of response is the measure.
2. Identification – a simple choice reaction time test. Speed of response is the measure.
3. One Card Back – a simple working memory test. Accuracy of response is the measure.
4. One Card Learning – a visual learning and memory test. Accuracy of response is the measure.

International Shopping List Task: The ISLT is a verbal learning and memory test assessing both immediate and delayed recall.

Functional Assessment Questionnaire: The FAQ has 10 items concerned with performing daily tasks necessary for independent living. Either a caregiver or informant or the subject provides performance ratings on 10 complex activities of daily living performed within the preceding 4 weeks.

Volumetric Magnetic Resonance Imaging: vMRI will be used to evaluate disease modification, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs.

**Pharmacokinetic Assessments**

Blood and CSF samples will be collected for the determination of the concentrations of E2609. Analyses of metabolite concentrations may be performed depending on emerging data from other studies with E2609.

**Pharmacodynamic, Pharmacogenomic and Other Biomarker Assessments**

Brain atrophy will be measured by vMRI: see Efficacy Assessments (above).

The soluble biomarkers Aβ(1-x), Aβ(1-42), total tau (t-tau), and p-tau will be measured in CSF. BACE1 levels and activity in CSF will also be measured.

Amyloid PET imaging will be used to confirm that all subjects eligible for progression to the Baseline Period of the study have amyloid deposition in the brain. Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted through to the time at which acceptable 18-month PET scans have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used.

Apolipoprotein E (*ApoE*) and *NAT2* genotyping/phenotyping will be conducted. *ApoE4* homozygous or heterozygous status and *NAT2* status will be used in the statistical analysis to determine the effects on treatment response and safety. Remaining genomic DNA may also be stored for up to 15 years to be used to examine the role of DNA sequence variability on the absorption, distribution, metabolism, and elimination of E2609, development of adverse events (AEs), as well as the underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single-nucleotide polymorphisms with PK, safety, or PD data.

**Safety Assessments**

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments. Routine safety assessments will include the monitoring and recording all AEs and serious AEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and dermatological

assessments at regular intervals. Information for AEs relating to abuse potential will be collected via a detailed narrative. Subjects reporting AEs relating to abnormal dreams or sleep-related events, or sleep terror will be questioned on the frequency and impact of these events.

Complete blood counts and lymphocyte subset absolute counts and percentages will be measured (by a centralized laboratory) every week for the first month, every 2 weeks for the next 2 months (Months 2 and 3) and monthly for the next 3 months (Months 4, 5, and 6). Thereafter they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits. Serum IgG, IgA, and IgM will be monitored monthly for the first 3 months, at 6, 12, and 18 months, and at both Follow-Up Visits.

Assessments by a dermatologist will be performed at baseline and at 3-month intervals during the Treatment Phase of the study. These assessments will specifically include evaluation of any areas of depigmentation or rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregivers/ informants will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so such AEs can be reviewed promptly.

Baseline and on-study blood, DNA, and CSF samples will be taken and stored from all subjects. These samples may be tested in the event that a subject develops AEs that warrant further investigation (eg, to test if a subject with a treatment-emergent infection was exposed to any suspected infective agents before treatment with study drug).

Safety brain MRI assessments will be performed at Screening, at 6, 12, and 18 months during the Treatment Phase of the study and at the final Follow-Up Visit. Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Full neurological examinations will be performed at Baseline, at 6, 12, and 18 months, and at both Follow-Up Visits, by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations. The neurological examinations will include muscle strength testing and assessment of cranial nerves including olfaction as well as other parts of the CNS.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments will include the ADAS-cog$_{14}$, MMSE, and CBB.

An assessment of suicidality using the C-SSRS will be performed at Screening and Baseline and at regular intervals throughout the treatment and Follow-Up periods of the study.

An ophthalmic examination will be conducted at Baseline. If the subject experiences visual disturbances during the course of the study, the subject will be referred to a specialist for a further ophthalmic examination including, where appropriate, a retinal examination.

A number of safety-related withdrawal criteria are specified for the study.

**Bioanalytical Methods**

Plasma and CSF concentrations of E2609 will be measured by a validated liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) in both CSF and plasma will be measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and post-screening analysis of CSF Aβ(1-42), tau, and p-tau will be performed using ELISAs.

BACE1 levels and activity may be measured using a customized assay. Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

**Statistical Methods**

All statistical tests will be based on the 5% (2-sided) level of significance, except for the Bayesian methods on the primary endpoint.

**Study Endpoints**

**Primary Endpoint**

- Change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects

**Secondary Endpoints**

Change from baseline in:

- Total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- CSF Aβ(1-x) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
- The derived ADCOMS at 18 months of treatment in mild AD subjects

**Exploratory Endpoints**

Change from baseline in:

- The derived ADCOMS at 12 months of treatment in MCI/Prodromal and mild AD subjects
- Total hippocampal volume at 12 and 18 months of treatment in mild AD subjects as measured by vMRI
- CSF Aβ(1-42) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects

- CSF Aβ(1-x) and Aβ(1-42) after 4 weeks and 18 months of treatment in mild AD subjects
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ in MCI/Prodromal and mild AD subjects
- CSF biomarkers of neurodegeneration (eg, tau and p-tau) at 18 months of treatment in MCI/Prodromal and mild AD subjects
- Plasma and CSF amyloid, and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild AD subjects
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and, 18 months in MCI/Prodromal and mild AD subjects as measured by vMRI
- Brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild AD subjects
- The population PK parameters of E2609 including the effect of intrinsic and extrinsic factors (including *NAT2* phenotype) in MCI/Prodromal and mild AD subjects

**Analysis Sets**

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set is the subset of subjects in the FAS who sufficiently comply with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 serum concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

**Efficacy Analyses**

***The MCI/Prodromal cohort:*** This study in the MCI/Prodromal cohort is based on Bayesian adaptive design. Frequent interim analyses will be performed to assess the probability of early success and futility and to make early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis. Key definitions relevant to the Bayesian aspects of the adaptive design are given below.

**Study Definitions**

- **Maximum Effective Dose ($d_{Max}$):** The dose that achieves the greatest treatment effect.

- **$ED_{90}$:** The lowest dose that achieves at least 90% of the $d_{Max}$ treatment effect in the derived ADCOMS.
- **Early Success:** The study in the MCI/Prodromal cohort will meet early success criteria if the probability that the $ED_{90}$ at 18 months of treatment achieves 25% improvement over placebo is at least 80%. Early success is achieved before all MCI/Prodromal subjects complete 18 months of treatment and can only be determined after at least 200 MCI/Prodromal subjects have been randomized. If early success is declared before full randomization, the randomization of new MCI/Prodromal subjects will stop but subjects already randomized into the study will receive the full 18 months of treatment (following confirmation from the Sponsor's Senior Management).
- **Futility:** The study in the MCI/Prodromal cohort will meet statistical futility criteria if the probability that the $ED_{90}$ is better than placebo by the clinically significant difference of 25% is less than 5% at 18 months of treatment. The statistical futility boundary is binding; if the statistical futility boundary is crossed the study will be considered to have failed.
- **Study Success:** The study in the MCI/Prodromal cohort will be considered a success if an $ED_{90}$ at 18 months treatment has at least an 80% probability of achieving 25% improvement over placebo at either an interim analysis or at the final analysis.

***The Mild AD cohort:*** The analysis of the Mild AD cohort is based on the group sequential design. Interim analyses in the Mild AD cohort will only be performed after the MCI/Prodromal cohort crosses the early success boundary. The early efficacy signal based on the change from baseline of ADCOMS at 18 months is defined as crossing the interim-analysis boundaries for overwhelming efficacy in the mild AD population. The O'Brien-Fleming (OF) boundaries based on Lan-DeMets alpha spending function will be used to assess overwhelming efficacy. The corresponding OF boundaries based on *P* values will be 0.076, 0.0221, and 0.0423 for the first, second, and final analyses, respectively, according to 2 planned interim analyses at the 60% and 80% information fraction.

**Analysis for the primary endpoint**

The primary analysis will be based on MCI/Prodromal subjects from the FAS with the prespecified censoring rule applied. The primary endpoint is the change from baseline to 18 months in the derived ADCOMS. The dose-response of the primary endpoint is modelled with a first-order normal dynamic linear model, where Normal and Inverse-Gamma priors are used. The primary efficacy analysis will calculate the Bayesian posterior probability that the dose identified is the most likely $ED_{90}$ dose that achieves 25% improvement over the placebo arm. At each interim analysis and the final analysis, 2 Bayesian probabilities will be summarized for each active dose: the probability it is the $ED_{90}$ dose and the probability of achieving 25% improvement over the placebo arm.

For the clinical efficacy data (ie, derived ADCOMS, MMSE, ADAS-cog, etc), subjects will be censored at the time of initiation of treatment with AChEIs or memantine, if they were not on these medications at the time of Baseline cognitive assessment (Visit 2), and will be censored at the time of dose adjustment of AChEIs or memantine if they were already on

stable treatment with these medications at the time of Baseline cognitive assessment (Visit 2). The value of the primary endpoint for censored subjects will be imputed using data up to the censoring time and Bayesian longitudinal modeling.

After unblinding, the primary endpoint will be analyzed using the Bayesian methods described above as well as conventional statistical methods. The following additional Bayesian analyses will be conducted as sensitivity analyses:

- The primary endpoint will be analyzed regardless of initiation of treatment, or dose adjustment, with AChEIs or memantine using the same Bayesian analysis method as primary analysis. This is an intent-to-treat analysis without any censoring.
- In case of early success, the primary analysis as well as the above sensitivity analyses will be repeated after all subjects have completed 18 months of treatment or have been lost to follow up.

Statistical methods for the final conventional analyses will use a mixed-effects model with repeated measures (MMRM) on the change from baseline in the derived ADCOMS at 18 months. The model will include treatment groups, randomization stratification variables (the presence or absence of ongoing treatment with AChEIs or memantine or both, and *ApoE4* status), and baseline ADCOMS as covariates. These analyses will be performed on the FAS as well as the per protocol set. In case of early success, the conventional analyses will also be performed using the data collected before the interim analysis.

**Analysis for the secondary endpoints**

***The MCI/Prodromal cohort***

An MMRM will be used to analyze the following secondary endpoints:

- Change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-x) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects. Data from early discontinuations will also be included.

Comparisons between each treatment group and placebo will be performed.

***The Mild AD cohort***

An MMRM will be used to analyze the change from baseline of derived ADCOMS at 18 months in mild AD. If there is no treatment group-by-population interaction in the overall study, the MMRM analysis will include all subjects (MCI/Prodromal or mild AD) in the overall study. Otherwise, the MMRM analysis will only include subjects in the mild AD cohort. The comparison between placebo and active doses will be performed within mild AD subjects regardless of subjects included in the MMRM analysis. Dunnett's method will be used to control for multiplicity due to multiple comparisons.

**Analysis for exploratory endpoints**

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in the derived ADCOMS at 12 months in MCI/Prodromal and mild AD subjects
- Change from baseline in total hippocampal atrophy at 12 and 18 months in mild AD subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-42) after 4 weeks and 18 months in MCI/Prodromal subjects. Data from early discontinuations will also be included.
- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) after 4 weeks and 18 months in mild AD subjects. Data from early discontinuations will also be included.
- Change from baseline in the clinical assessments: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months in MCI/Prodromal and mild AD subjects
- Change from baseline in plasma and CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild AD subjects
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and 18 months as measured by vMRI in MCI/Prodromal and mild AD subjects

A linear mixed-model will be used to analyze the following exploratory endpoints:

- Change from baseline in brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild AD subjects
- Change from baseline in CSF biomarkers of neurodegeneration (eg, tau, p-tau) at 18 months of treatment in MCI/Prodromal and mild AD subjects

Data from early discontinuations will also be used as appropriate. Comparisons between each treatment group and placebo will be performed.

A linear mixed-model with repeated measures will be used to determine the relationship between the following endpoints:

- Change from baseline in the derived ADCOMS score and the change from baseline in biomarkers in CSF at 18 months in MCI/Prodromal and mild AD subjects
- Change from baseline in the derived ADCOMS score and change from baseline in imaging biomarkers (hippocampal, whole brain, and total ventricular volumes) at 12 and 18 months in MCI/Prodromal and mild AD subjects

*ApoE* status for heterozygous and homozygous E4 carriers will be included in the model to assess the effect of *ApoE* status in this relationship.

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). CSF Aβ(1-x), Aβ(1-42), t-tau, p-tau, and BACE1 will be assessed and data will be presented graphically. Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status. Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels and exposure to E2609 in plasma and CSF will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. Additionally, the relationship between CSF exposure to E2609 and the derived ADCOMS at 18 months, and the relationship between CSF exposure to E2609 and the change from baseline for 18 months in the ADAS-cog, the CDR, and the MMSE will be explored graphically. Any emergent relationship will be explored through population PK/PD modeling.

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT 2* phenotype of subjects enrolled in this study. Further information is in the "Pharmcodynamic, Pharmacogenomic, and Other Biomarker Assessments" section. Details of pharmacogenomic testing may be provided and reported separately.

**Safety Analyses**

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, and vital sign measurements will be summarized by treatment group using descriptive statistics.

<u>Lymphocyte Subsets</u>

Lymphocyte subsets (ie, CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages]) and regulatory T cells will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically

over time by dose. Serum IgG, IgM, IgA will be measured and summarized in the same manner as other laboratory parameters.

**Interim Analyses**

***The MCI/Prodromal cohort***

Oversight of the Bayesian interim analyses and response adaptive randomization will be conducted by an independent committee that has expertise with Bayesian adaptive design in clinical studies. An unblinded external independent analysis group will provide the interim analysis outcomes to the committee at each interim analysis. The committee will ensure the integrity of the interim analysis and response adaptive randomization process through review of efficacy data. In addition, the committee will act in an independent advisory capacity to monitor the Bayesian interim analysis outcomes according to the early success and futility boundaries prespecified in the protocol. The committee will not be charged with any subject safety issues; this will remain the responsibility of the DSMB. The DSMB will continue to monitor the safety aspects of the study throughout Stage A and Stage B. The study may be stopped for safety at any time.

An interim safety analysis will be conducted when the first 60 MCI/Prodromal subjects have completed 12 weeks of treatment. The first Bayesian adaptive interim analysis will be conducted when 100 MCI/Prodromal subjects have been randomized into the study (ie, 60 subjects from Stage A and the first 40 subjects from Stage B of the study). Further interim efficacy analyses will be conducted after each additional 50 MCI/Prodromal subjects have been randomized, up to a maximum of 500 MCI/Prodromal subjects (ie, at 100, 150, 200, 250, 300, 350, 400, 450, 500 subjects randomized). If the study reaches full randomization, additional interim analyses will be conducted every 3 months until all subjects complete 18 months of treatment. The study will be monitored for futility at each interim analysis. Starting at the 200 subjects' interim analysis, the study will be monitored for success at each interim analysis. Each interim analysis will be conducted on data for the derived ADCOMS.

If the predefined early success criteria are met during the recruitment period, further recruitment and enrollment of MCI/Prodromal subjects into the study will stop (following confirmation from the Sponsor's Senior Management) and all currently randomized subjects will complete the full 18 months of treatment. No further interim analyses will be conducted after achieving early success.

If the predefined threshold for futility is reached, no additional subjects will be randomized into the study and the treatment of subjects already randomized into the study will stop and the study will be declared as "failed". All subjects will be monitored for safety for 3 months following their last dose.

If neither early success nor futility is reached and the study reaches full randomization, all subjects will complete 18 months of treatment. Interim efficacy analyses will be conducted every 3 months after full randomization is reached to assess futility and early success until all

subjects complete 18 months of treatment. After full randomization, all study subjects will stop treatment only in the event of futility.

***The Mild AD cohort***

A group sequential design will be used for the mild AD cohort. This design includes 3 looks, 2 interim looks (when 60% and 80% information fractions are achieved) and 1 final look. Interim analyses will be performed after the MCI/Prodromal cohort crosses the early success boundary. The corresponding efficacy boundaries will be 0.076, 0.022, and 0.0423 for the first, second, and final analyses, respectively. If the actual information fraction during the interim analyses is different from 60% or 80% at the interim, the efficacy boundaries will be adjusted based on the actual information fraction. If early success in the MCI/Prodromal cohort is not achieved before the final analysis that is performed when all subjects have completed 18 months treatment, then only a final analysis will be performed in mild AD subjects. In the event of futility in the MCI/Prodromal cohort, an analysis will be performed for the mild AD cohort based on the data for mild AD subjects available at that time.

**Adaptive randomization in the MCI/Prodromal cohort**

Randomization to placebo or 1 of 3 dose groups of E2609 will be fixed for the first 100 subjects randomized in the study (1:1:1:1; placebo to each of the 3 active doses [60 patients in Stage A and the first 40 patients in Stage B]). Randomization probabilities to each treatment group will be updated at each interim analysis, such that the randomization probability will be increased for the placebo group and dosage groups that represent the potential target dose ($ED_{90}$), and simultaneously decreased for other active arms. Randomization in the Mild AD cohort will remain at a fixed schedule throughout Stage B.

Within the 2 clinical populations (MCI/Prodromal and mild AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no).

**Sample Size Rationale**

***Sample Size Rationale in the MCI/Prodromal cohort***

Primary endpoint – derived ADCOMS: The sample size and design characteristics to test the hypothesis for the primary objective based on the primary endpoint were determined by means of simulations. Extensive study simulations have shown that a total of 500 subjects will be sufficient to demonstrate that the most likely $ED_{90}$ dose achieves a 25% improvement over placebo with a probability of at least 80% in the interim and final analyses. There is at least a 90% probability of study success for the dose response scenarios where treatment was considered to have a clinically meaningful treatment effect. Simulations have also shown that if there is no obvious dose effect, the probability of falsely claiming superiority to placebo is at most 5%.

For each of the 4 treatment groups (3 active doses and placebo), the final number of subjects per group will differ depending on the observed interim treatment responses.

vMRI: The null hypothesis is that there is no difference between active dose and placebo. There are 3 null hypotheses corresponding to 3 active doses. The alternative hypothesis is that at least 1 null hypothesis is false (1-sided). The null hypotheses will be tested using Dunnett's method with 1-sided alpha of 0.05. The statistical power was estimated through simulation for a moderate dose-response assumption that the percent reduction in change from baseline of total hippocampal volume compared with placebo would be 15%, 20%, and 25% corresponding to the 3 doses, respectively. The estimated power for actual planned study sample size is 78% at 18 months assuming an attrition rate of 20% at 18 months. Under a stronger dose-response assumption (ie, the percent reduction in change from baseline of total hippocampal volume compared with placebo is twice as much as that in the moderate dose-response assumption), the estimated power is at least 99% at 18 months.

Amyloid PET: The null and alternative hypotheses and statistical test are the same as those for vMRI. To estimate the sample size for the amyloid PET imaging subgroup at 18 months, a common SD of change from baseline was estimated at 0.33 and a reasonable mean difference between treatment and placebo was estimated as 0.25 (standardized uptake value ratio [SUVR]). Assuming a moderate dose-response, the best dose would achieve a difference of 0.25 (SUVR) and the middle and low doses would achieve a difference of 0.2 and 0.15 (SUVR), respectively, it would require a total of 100 subjects from all 4 arms at 18 months to achieve 80% power.

***Sample Size Rationale for the Mild AD Cohort***

ADCOMS at Month 18: The null hypothesis is that there is no difference between active dose and placebo. There are 2 null hypotheses corresponding to 2 active doses. The alternative hypothesis is that at least 1 null hypothesis is false. The null hypotheses will be tested using Dunnett's test with 2-sided alpha of 0.05 as described for the mild AD cohort in the secondary analysis section. The statistical power was estimated through simulation for the dose-response assumption that the percent reduction in change from baseline of ADCOMS at 18 months compared with placebo would be 33% and 50% corresponding to the 2 doses, respectively. The estimated power for the actual planned 200 mild AD subjects is at least 80% assuming a 2-sided alpha of 0.05.

# 3 TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES



## LIST OF IN-TEXT FIGURES



## LIST OF APPENDICES

# 4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| Aβ | amyloid β |
| Aβ(1-x) | amyloid β (1-x) (ie, the amyloid β monomer from amino acid 1 to x [eg 1-42]) |
| AChEI | Acetylcholinesterase inhibitor |
| AD | Alzheimer's disease |
| ADAS-cog | Alzheimer's Disease Assessment Scale - cognitive subscale |
| ADCOMS | Alzheimer's Disease Composite Score |
| AE | Adverse Event |
| ApoE | Apolipoprotein E |
| AUC | area under the concentration x time curve |
| $AUC_{(0\text{-}24h)ss}$ | area under the concentration x time curve at steady state from time zero to 24 hours |
| BACE1 | Beta-amyloid converting enzyme 1 |
| BP | blood pressure |
| bpm | beats per minute |
| CBB | CogState Brief Battery |
| CBP | childbearing potential |
| CDR | Clinical Dementia Rating |
| CES2 | carobxyesterase-2 |
| CFR | Code of Federal Regulations |
| $C_{max,ss}$ | maximum plasma concentration at steady state |
| CNS | central nervous system |
| CRA | clinical research associate |
| CRF | case report form |
| CRO | contract research organization |
| CSF | cerebrospinal fluid |
| $C_{ss,av}$ | average steady-state concentration |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CTA | Clinical Trial Agreement |
| CYP | cytochrome P450 |
| $d_{Max}$ | Maximum effective dose |
| DSMB | data safety monitoring board |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| ED | early discontinuation |

| Abbreviation | Term |
|---|---|
| $ED_{90}$ | lowest effective dose that achieves 90% of the greatest treatment effect |
| ELISA | enzyme-linked immunosorbent assay |
| FAQ | Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire) |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FLAIR | fluid-attenuated inversion recovery |
| GCP | Good Clinical Practice |
| GDS | Geriatric Depression Scale |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |
| HCVAb | hepatitis C virus antibody |
| HSV | herpes simplex virus |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ID | identifier |
| IEC | Independent Ethics Committee |
| Ig | immunoglobulin (eg, IgA, IgG, IgM) |
| IRB | Institutional Review Board |
| ISLT | International Shopping List Task |
| IxRS | interactive voice and web response system |
| LLN | lower limit of normal |
| LNH | low/normal/high |
| LP | lumbar puncture |
| MAD | multiple ascending dose |
| MCI | mild cognitive impairment |
| MCI/Prodromal | Mild Cognitive Impairment due to Alzheimer's Disease/ Prodromal Alzheimer's Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mild AD | mild dementia due to Alzheimer's Disease |
| MMRM | mixed-effects model with repeated measures |
| MMSE | Mini Mental State Examination |
| MRI | magnetic resonance imaging |
| NAT2 | N-acetyltransferase 2 |
| NIA-AA | National Institute on Aging-Alzheimer's Association |

| Abbreviation | Term |
|---|---|
| OF | O'Brien-Fleming |
| PD | Pharmacodynamic(s) |
| PET | positron emission tomography |
| PGx | Pharmacogenomic(s) |
| PK | Pharmacokinetic(s) |
| PP | per protocol |
| PRN | Pro re nata |
| PT | preferred term |
| p-tau | phosphorylated-tau |
| QD | once daily |
| QTc | corrected QT interval |
| QTcF | QTc interval calculated using Fridericia's formula |
| R | randomization |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reaction |
| SUVR | standardized uptake value ratio |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |
| TEMAV | treatment-emergent markedly abnormal laboratory values |
| t-tau | total tau |
| ULN | upper limit of normal |
| UNS | unscheduled |
| vMRI | volumetric magnetic resonance imaging |
| WHO DD | World Health Organization Drug Dictionary |
| β-hCG | beta-human chorionic gonadotropin |

Study References: On first use, the full study code will be used (eg, E2609-G000-202) with a shortened form in brackets (Study 202); thereafter, the shortened form is used.

# 5 ETHICS

## 5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA][s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigators or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

## 5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (CFR) (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

- European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved European Union member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

## 5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject and the identified caregiver or informant, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if the identified caregiver or informant is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject and the identified caregiver or informant, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified caregiver or informant should also consent to supporting the subject's participation in the study and will be provided with a separate written ICF for his or her participation in the study, to be signed before he or she participates in any further aspects of the study.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified caregiver or informant must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified caregiver or informant will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified caregiver or informant should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

# 6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 125 investigational sites globally (25 sites in the United States for Stage A and 125 sites globally for Stage B).

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

# 7 INTRODUCTION

At this time, there is no cure for Alzheimer's disease (AD), no known way of slowing down the progression of this disease, and no approved treatment available to reverse the deterioration. There is, therefore, an urgent unmet medical need for drugs that slow or prevent disease progression. Beta-amyloid converting enzyme 1 (BACE1) is a key enzyme responsible for the production of amyloid β (Aβ) peptides and plaque formation, and several reports have described elevated levels of BACE1 in AD brains (Coulson, et al., 2010, Lu, et al., 2012). Once amyloid plaques form, Aβ causes BACE1 levels to increase further, thus accelerating Aβ generation and plaque growth via a positive feedback loop. Therefore, BACE1 is a promising target for modifying or treating AD.

It is now widely accepted that mild cognitive impairment (MCI) due to AD and mild AD dementia are stages on a single disease spectrum, which follows an Alzheimer's pathological cascade. Recent consensus papers from the international workgroups of the National Institute on Aging-Alzheimer's Association (NIA-AA), have endorsed this hypothesis (Albert, et al., 2011; Jack, et al., 2011; McKhann, et al., 2011; Sperling, et al., 2011).

From a clinical standpoint, demonstration of an effect on slowing disease course is hampered by the lack of sensitive tools for detecting relatively small changes in progression or treatment effect especially in early disease. In addition, drugs that are expected to slow disease progression require longer study durations to ensure adequate separation from placebo. These challenges have resulted in the use of biomarkers as surrogates for clinical effect in Phase 2 studies, in order to facilitate the development process for disease modifying agents. However, subsequent Phase 3 AD studies based solely on biomarker findings in Phase 2 have failed to show clinical effect, due, in part, to the fact that biomarkers may not predict clinical outcomes for potential disease modifying agents. These findings underscore the need for innovative approaches to clinical study design for measuring the effect of treatment.

E2609 is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, E2609 inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in cerebrospinal fluid (CSF) and plasma (rat, guinea pig, and monkey). In humans, E2609 has been shown to inhibit BACE1 enzyme activity in CSF and lower the levels of Aβ, including amyloid beta monomer from amino acid 1 to x (Aβ[1-x]), Aβ(1-40) and Aβ(1-42), in CSF both in vitro and in vivo. See the Investigator's Brochure for additional information. The target indication for E2609 is therefore treatment and disease modification of AD.

The present clinical study represents the sole Phase 2 study for the E2609 program, and is designed to establish Proof of Concept in subjects with Mild Cognitive Impairment due to Alzheimer's Disease/Prodromal Alzheimer's Disease (referred to as MCI/Prodromal throughout the protocol). The study also allows investigation of efficacy in subjects with mild dementia due to Alzheimer's Disease (referred to as mild AD throughout the protocol) to determine whether the effects of E2609 in this later stage population are comparable with those established in the MCI/Prodromal population within this same study. In the MCI/Prodromal population, Bayesian response adaptive randomization design is used with

frequent interim analyses to continually update randomization allocation based on emerging clinical endpoint data. This approach allows for ongoing assessment of drug futility or evidence of early success and can mitigate the risks associated with larger and longer studies required to demonstrate clinical efficacy by leading to more efficient study termination or early advancement to a Phase 3 program. Results from this study will guide both the decision to move into Phase 3 development and the selection of the dose strengths to be taken into Phase 3. Moreover, this study is intended to be supportive for registration in the MCI/Prodromal population.

In the MCI/Prodromal population, this study will compare placebo and 3 oral doses of E2609 (5 mg, 15 mg and 50 mg) administered once daily (QD) for 18 months. In the mild AD population, this study will compare placebo and 2 oral doses of E2609 (15 mg and 50 mg) administered QD for 18 months. To date, the longest duration of dosing with E2609 is 14 days (multiple ascending dose [MAD] Study E2609-A001-002 [Study 002]).

This study (E2609-G000-202 [Study 202]) will comprise 2 stages: Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 in the United States sites only, before expanding enrollment to a larger and more global population of subjects in Stage B. This design will allow close monitoring of safety by an independent data safety monitoring board (DSMB), including a formal safety review as soon as the first 60 randomized subjects have completed 12 weeks of treatment or have withdrawn from the study. The study also includes a number of exclusion criteria, specific blinded safety monitoring procedures and safety withdrawal criteria in light of the preclinical and clinical safety data collected to date following administration of E2609.

## 7.1 Nonclinical and Clinical Safety Data

The toxicity of E2609 has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomologus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by E2609 in a clinical setting. Further details of the nonclinical data to date with E2609 can be found in the Investigator's Brochure.

The clinical program to date includes 6 Phase 1 studies:

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, single ascending dose (SAD) study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled MAD study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the

14 days of dosing so as to assess the pharmacokinetic (PK) levels of E2609 and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of E2609. It also investigated the effects of E2609 on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of $^{[14C]}$E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of E2609 under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) was a randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with E2609. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with E2609. In elderly subjects treated with 50 mg of E2609, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTc interval calculated using Fridericia's formula (QTcF) from baseline (14.9 msec at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of E2609 might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that E2609 altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of E2609. A single dose of E2609 up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, E2609 administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment

by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of E2609 on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carobxyesterase-2 [CES2]) caused a mild increase (by approximately 70%) of the area under the concentration x time curve (AUC) of E2609. Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of E2609. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of E2609 when coadministered with E2609 but not when dosed at least 2 hours apart from E2609. E2609 (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of E2609. Based on these results, it is not considered necessary to impose restrictions during E2609 treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors, or CES2 inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications which are inducers of CYP450 enzymes.

# 8 STUDY OBJECTIVES

## 8.1 Primary Objectives

The primary objectives are:

1. To evaluate the efficacy of daily dosing with 3 doses of E2609 compared with placebo by establishing the lowest effective dose that achieves 90% of the greatest treatment effect ($ED_{90}$) for E2609 on the derived Alzheimer's Disease Composite Score (ADCOMS) at 18 months of treatment in subjects with MCI/Prodromal
2. To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with mild AD

## 8.2 Secondary Objectives

The secondary objectives are:

1. To evaluate the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects, as measured by volumetric magnetic resonance imaging (vMRI)
2. To evaluate the effect of E2609 compared with placebo on Aβ(1-x) in CSF after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
3. To evaluate the efficacy of E2609 compared with placebo on the derived ADCOMS at 18 months in mild AD subjects

## 8.3 Exploratory Objectives

The exploratory objectives are:

1. To explore the effect of E2609 compared with placebo on the derived ADCOMS following 12 months of treatment in MCI/Prodromal and mild AD subjects
2. To explore the effect of E2609 compared with placebo on total hippocampal atrophy at 12 and 18 months of treatment in mild AD subjects, as measured by vMRI
3. To explore the effects of E2609 compared with placebo on Aβ(1-42) in CSF after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
4. To explore the effects of E2609 compared with placebo on Aβ(1-x) and Aβ (1-42) in CSF after 4 weeks and 18 months of treatment in mild AD subjects

5. To explore the effects of E2609 compared with placebo on clinical status at various time points during 18 months of treatment, and during post treatment follow-up, in MCI/Prodromal and mild AD subjects, by assessment of:
   a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
   b. The Clinical Dementia Rating (CDR) scale
   c. The Mini-Mental State Examination (MMSE)
   d. The CogState Brief Battery (CBB)
   e. The Functional Assessment Questionnaire (FAQ; (also known as the Functional Activities Questionnaire)
   f. The International Shopping List Task (ISLT)
6. To explore the effects of E2609 compared with placebo on various biomarkers in MCI/Prodromal and mild AD subjects. Biomarkers to be explored include:
   a. CSF biomarkers of neurodegeneration (eg, tau, phosphorylated-tau [p-tau]) after 18 months of treatment
   b. Plasma and CSF amyloid, and CSF BACE1 measurements during 18 months of treatment and during post treatment follow-up
   c. vMRI measurements including left and right hippocampal volume, whole brain volume, and total ventricular volume at 6, 12, and 18 months of treatment and during post treatment follow-up
   d. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)
7. To characterize the population PK of E2609 in MCI/Prodromal and mild AD subjects, and to examine the effect of intrinsic and extrinsic factors (including N-acetyltransferase 2 [*NAT2*] phenotype) on the PK
8. To explore the relationship between the treatment effects of E2609 on the ADCOMS and its effects on CSF amyloid, CSF BACE1, CSF tau, and vMRI in MCI/Prodromal and mild AD subjects

# 9 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan

Study 202 is a multicenter placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with MCI/Prodromal AD or mild AD.

A common set of inclusion criteria, consistent with the NIA-AA clinical research criteria for MCI due to AD or mild AD, will be required for all subjects. In addition, the MCI due to AD population will also qualify under the research criterion for "Prodromal AD." As the non-demented subjects will fulfill the criteria for both MCI due to AD and Prodromal AD they will be identified as MCI/Prodromal subjects in this protocol. The diagnosis of MCI/Prodromal AD or mild AD will be based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria.

The study will be conducted in 2 stages, Stage A and Stage B. Stage A will include an interim evaluation of the safety and tolerability of chronic dosing with E2609 (at least 12 weeks) in MCI/Prodromal subjects, before expanding enrollment to include a larger population of MCI/Prodromal subjects in Stage B (maximum of approximately 500 subjects across both stages). In addition, during Stage B of the study, subjects with mild AD will be recruited into a separate cohort (approximately 200 subjects). All MCI/Prodromal subjects will be included in the primary efficacy evaluation irrespective of whether they were recruited into Stage A or Stage B of the study.

Both Stage A and Stage B of the study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase (up to 60 days) will consist of a Screening Visit and a Baseline Visit. Screening assessments will be organized into 4 tiers; see Section 9.5.2.2, Table 6, and Figure 2. All screening assessments must be completed, and eligibility to continue to the Baseline Period confirmed, before any baseline assessments commence. Following successful completion of the Prerandomization Phase, eligible subjects will be randomized and will enter the Randomization Phase, which will consist of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks).

MCI/Prodromal subjects will be randomized to 4 treatment groups (E2609 at 3 doses or placebo, with an initial ratio of 1:1:1:1) and this recruitment will take place during both Stage A and Stage B. Bayesian adaptive randomization will be used in Stage B in the MCI/Prodromal cohort. Subjects with mild AD who are recruited in Stage B will be randomized to 3 treatment groups (E2609 at 2 doses or placebo).

An overview of the study design is presented in Figure 1.

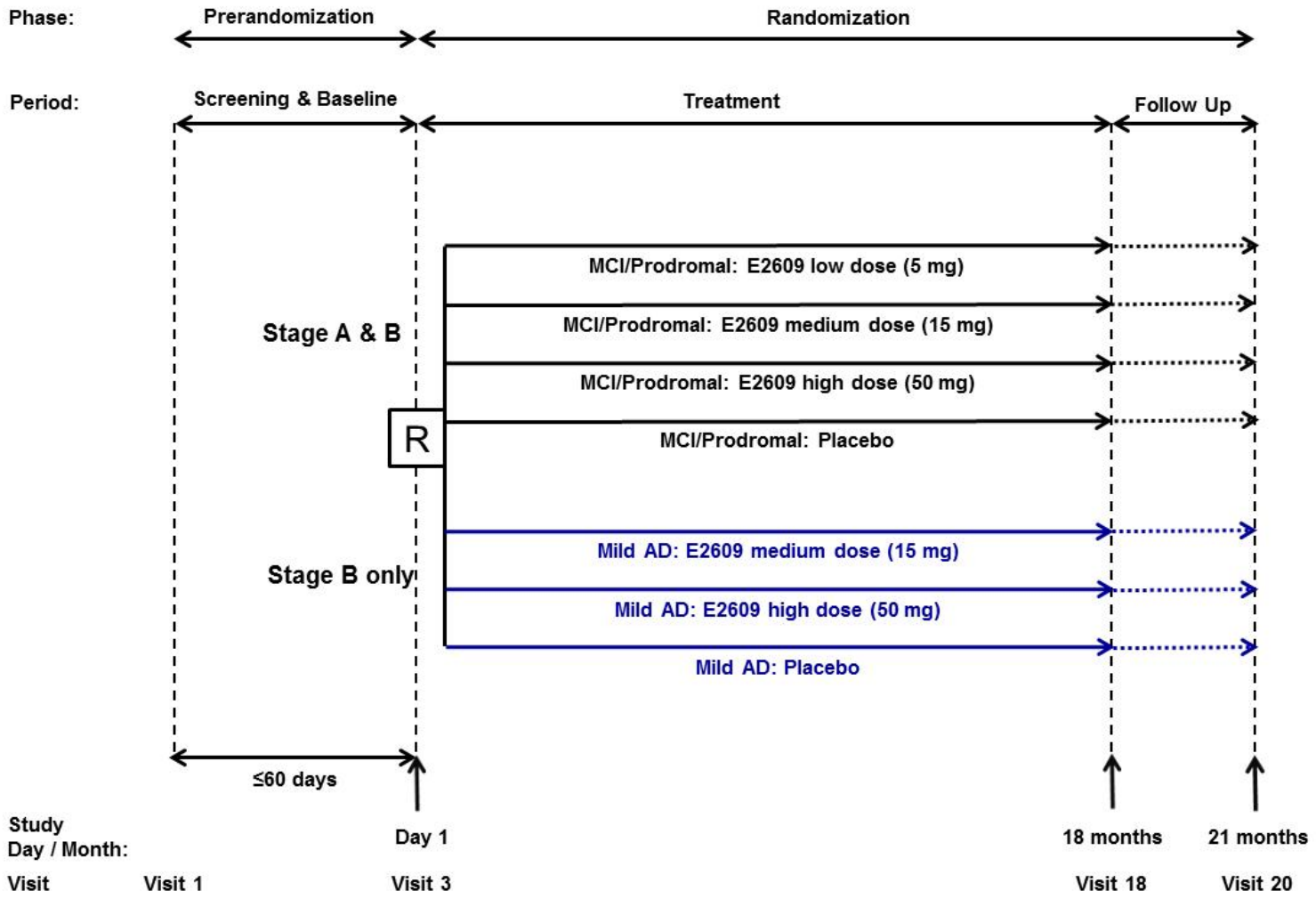



**Figure 1 Design of Study 202**

R = randomization.

**Stage A**

Stage A of the study will be limited to approximately 25 clinical centers in the United States. Stage A will enroll 60 eligible MCI/Prodromal AD subjects who will be randomized 1:1:1:1 to 4 treatment groups. There will be no Bayesian adaptation during Stage A of the study. In addition to the placebo group, 3 doses of E2609 will be used to reduce CSF Aβ levels by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, respectively, at steady state. PK/PD modeling shows these doses should achieve these targets when administered QD with food and will be confirmed or adjusted based on the 4-week assessment of CSF Aβ(1-x) (see Section 9.4.4).

During Stage A, safety data will be monitored in a blinded fashion on a regular basis. In addition, approximately every 3 months from the time the first subject is randomized during Stage A of the study, an independent DSMB (including at least 1 immunologist) will review all safety data in an unblinded manner. The DSMB will make recommendations to Eisai after each review as to whether any change(s) to the study are necessary. Unless the DSMB recommends otherwise, randomization of subjects into Stage A of the study will continue until 60 MCI/Prodromal subjects have been randomized and dosed.

After 60 MCI/Prodromal subjects in Stage A have completed 4 weeks of treatment, an interim analysis of the E2609 PK and PD profiles will be used to confirm the E2609 doses to be used for Stage B of the study (see Section 9.4.4).

Once 60 MCI/Prodromal subjects in Stage A have completed at least 12 weeks of treatment, an interim safety analysis will be conducted by Eisai and the DSMB. Subjects in Stage A will continue study drug while the DSMB reviews all the available safety data, but randomization of additional subjects will not take place (ie, recruitment into Stage B will not commence) until the safety analysis is completed by the DSMB. At the time of this interim safety analysis, some subjects will have more than 12 weeks of safety data.

**Stage B**

Stage B of the study will start after the DSMB safety review of Stage A has shown acceptable safety and tolerability of E2609 and after the doses of E2609 to be used in Stage B are confirmed. Based on data from Stage A, the protocol will be reviewed and may be amended before beginning Stage B. Safety data from Stage B will continue to be reviewed by the DSMB (approximately every 3 months) until recruitment in the study is completed; following this the DSMB will meet approximately every 6 months.

Stage B of the study will be conducted globally and will enroll, randomize, and dose up to an additional 440 eligible MCI/Prodromal subjects; the final total number will depend upon whether the prespecified criteria for either early success or futility are met. In addition, a separate cohort of approximately 200 mild AD subjects will be randomized and dosed during Stage B.

Both population cohorts will include separate placebo groups. The MCI/Prodromal cohort will include 3 doses of E2609 (5 mg, 15 mg, and 50 mg QD), whereas the mild AD cohort will only include 2 doses of E2609 (15 mg and 50 mg QD).

Bayesian adaptive randomization will be used in the MCI/Prodromal cohort during Stage B of the study. The first 40 MCI/Prodromal subjects recruited into Stage B will be randomized according to a fixed schedule (1:1:1:1; placebo: 5 mg E2609: 15 mg E2609: 50 mg E2609) and the remaining subjects in the MCI/Prodromal cohort will be randomized according to response adaptive randomizations based on the ADCOMS results using the Bayesian interim efficacy analyses. The mild AD subjects will be randomized according to a fixed schedule (1:1:1 placebo; 15 mg E2609; 50 mg E2609) throughout Stage B of the study.

Interim efficacy analyses are planned and are discussed in Section 9.7.3.

### 9.1.1 Prerandomization Phase

The Prerandomization Phase includes a Screening Visit and a Baseline Visit. All Screening Visit assessments must be completed and eligibility to progress must be confirmed before any Baseline Visit assessments are performed. All Screening Visit and Baseline Visit assessments must be completed within 50 days and a window of 7 to 10 days is to be observed between the completion of all Baseline Visit assessments and randomization into the study at Visit 3. Thus, the Prerandomization Phase will last for up to 60 days. The series of assessments conducted during this phase will determine eligibility for randomization into the study.

Inclusion criteria are discussed in Section 9.1 and detailed in Section 9.3.1. Before randomization the clinician will provide a judgment on the classification of a subject as either MCI/Prodromal (eligible for Stage A and Stage B) or likely mild AD (eligible for Stage B only). This judgment may be discussed and reviewed with the Sponsor or Sponsor's representative, as necessary.

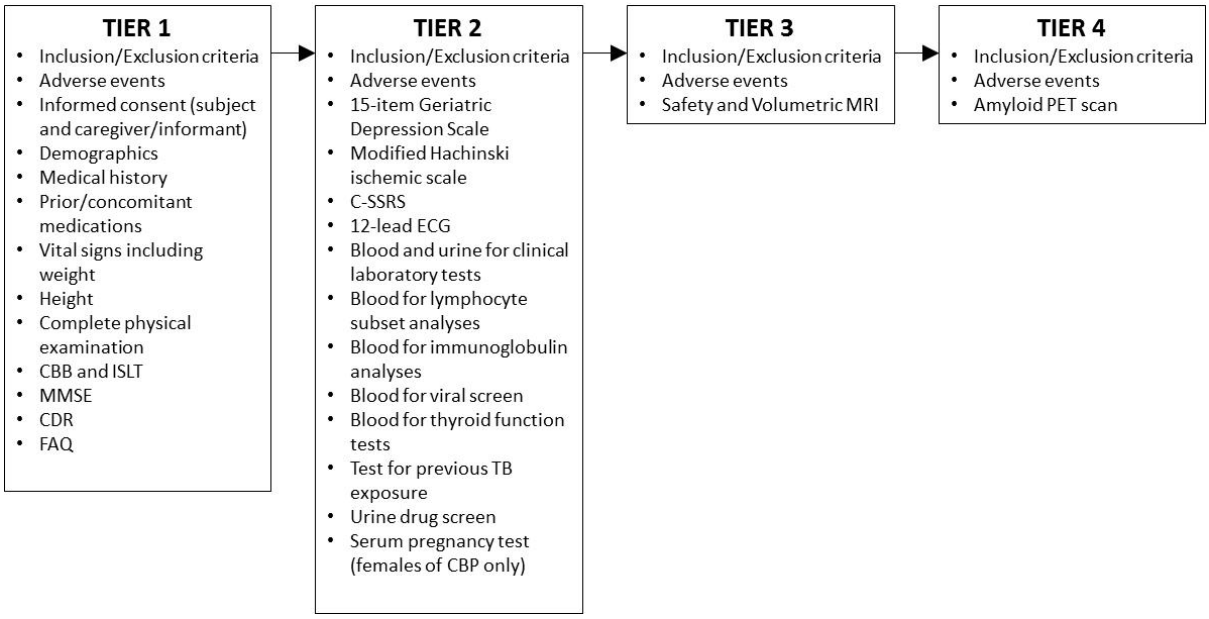
#### 9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and caregiver or informant, and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained from both the subject and the caregiver or informant. The caregiver or informant needs to be present at this visit.

Study site personnel will interview the subject and caregiver or informant to obtain demographic and clinical information as described in Table 6, and will review inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2 and perform any required assessments in order to complete these criteria. Prior medications and medications currently being taken by the subject will be reviewed (see Section 9.4.7). The Screening Disposition

electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

Clinical assessments for eligibility will be conducted during the Screening Visit as described in Table 6 and Figure 2. Every effort should be made to conduct these assessments in the morning, but if this is not possible, they should be conducted at the same time of day at all subsequent visits. The screening assessments/procedures have been organized into 4 distinct tiers (Table 6 and Figure 2). All assessments/procedures in each tier should be completed, and eligibility to continue screening in the study confirmed, before any assessments/procedures from the next tier commence.




## Figure 2 Assessments to be Performed at Screening by Tier

CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), ISLT = International Shopping List Task (immediate and delayed recall), MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PET = positron emission tomography, TB = tuberculosis.

Cognitive assessments (Tier 1) are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). The order of assessments is: MMSE, CDR, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall) at Screening. The investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session (Tier 3).

Amyloid PET imaging will be used to confirm all subjects have amyloid deposition in the brain (Tier 4).

#### 9.1.1.2 Baseline Period

All Screening Visit assessments must be completed (and eligibility to progress confirmed) before any Baseline Visit assessments are performed. The Baseline Visit assessments (per Table 6 and Section 9.5.1.2) are to be completed as soon as possible after completion of the final Screening Visit assessment (ie, PET scan) such that all Screening Visit and Baseline Visit assessments are completed within 50 days.

Inclusion and exclusion criteria will again be reviewed, vital signs including weight will be recorded, and a 12-lead ECG will be conducted in triplicate. A routine physical examination will be conducted and a dermatological assessment and neurological examination will be performed. A urine pregnancy test will be conducted for females of childbearing potential. Blood will be collected from all subjects for clinical chemistry and hematology, lymphocyte subset analyses, Ig analyses, and PD assessments. Blood samples will be collected and stored for determination of a subject's previous exposure to infective pathogens in the event of AEs that warrant further investigation occurring at a later point in the study. Psychometric assessments will be administered to the subject in the order stated in Table 6. The caregiver or informant needs to be present at this visit. The Columbia Suicide Severity Rating Scale (C-SSRS) will also be administered (Section 9.5.1.5.11).

CSF will be obtained at this visit for PK and PD assessments (see Section 9.5.1.5.3).

Blood will be collected from all subjects for pharmacogenomic (PGx) analyses of apolipoprotein E (*ApoE4*) and the *NAT2* phenotype of subjects enrolled in the study (see Section 9.7.1.7.2).

### 9.1.2 Randomization Phase

Subjects who complete the Baseline Visit assessments, and are eligible based on the inclusion and exclusion criteria (see Section 9.3.1 and Section 9.3.2), will begin the Randomization Phase within 7 to 10 days following completion of the Baseline Visit assessments.

The Randomization Phase will consist of a Treatment Period of 78 weeks duration and a Follow-Up Period of 12 weeks after the last dose of study drug.

#### 9.1.2.1 Treatment Period

Subjects will be randomized at the beginning of the Treatment Period and will receive study drug or placebo, to be administered orally QD with food. Double-blinding to study drugs will be in effect throughout the Treatment Period. The dose for a subject will not be changed during the study. However, dose adjustment for Stage B may be considered and subjects already randomized to a dose that needs to be adjusted will be switched to continue their treatment at the new adjusted dose.

Safety withdrawal criteria for this study are detailed in Section 9.3.3.

Subjects will attend the study site every week for the first 4 weeks after beginning study drug, then fortnightly until 12 weeks have elapsed since first dose. Visits will then be conducted at 16, 20, 26, 39, 52, 65, and 78 weeks after the first dose.

#### 9.1.2.2 Early Discontinuation

Subjects who discontinue taking study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug. Subjects who discontinue study drug prematurely will also be scheduled to return to the study site to undertake limited efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, CBB, and ISLT) at Week 53 (Visit 16) and Week 79 (Visit 18), if these 2 visits have not already been performed.

#### 9.1.2.3 Follow up

All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug (Visit 19) and a second 12 weeks after the last dose of study drug (Visit 20). If clinically indicated, more frequent safety assessments can be conducted as part of unscheduled visits during the posttreatment Follow-Up period.

The end of the study will be defined as the date of the clinical database lock (ie, when all study data are collected and data validation is completed).

As required by some regulatory agencies, the following estimates are provided:

- The study will begin in Nov 2014 and will end on or before Aug 2019.
- The maximum estimated period for each subject on study is anticipated to be approximately 2 years.

## 9.2 Discussion of Study Design, Including Choice of Control Groups

### 9.2.1 Overview

The design of this study allows Proof of Concept to be established in subjects with MCI/Prodromal AD. The study also allows investigation of efficacy in subjects with mild AD to determine whether the effects of E2609 in this later stage population are comparable with those established in the MCI/Prodromal population within this same study (see Section 9.2.3 for discussion of the Bayesian design used in this study).

The inclusion criteria for the MCI/Prodromal cohort will be consistent with the NIA-AA criteria for MCI due to AD (Albert, et al., 2011) and will also meet the definition of Prodromal AD per Dubois et al., 2010 (see Section 9.2.2).

There is no active or positive control for this study as at this time, there is no cure for AD, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary efficacy tool for this Proof of Concept study is the composite scale ADCOMS (change from baseline in the derived ADCOMS at 18 months). The ADCOMS (Hendrix, et al., 2012) represents a novel composite approach integrating components of well established tools (ADAS-cog, MMSE, and CDR) to improve sensitivity to disease progression and treatment effects in subjects with AD (see Section 9.2.4).

Secondary efficacy endpoints include a biomarker of neuronal degeneration (shrinkage of neurons), which is the change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI; an amyloid biomarker, which is the change from baseline in CSF Aβ(1-x) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects; and a cognitive and functional assessment, which is the change from baseline in the derived ADCOMS at 18 months of treatment in mild AD subjects. Exploratory endpoints including assessments of efficacy, safety and other biomarkers are also included.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

### 9.2.2 Rationale for Study Population

By the time AD progresses to dementia, with loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack, et al., 2010). There is a growing consensus within the AD field that it may be necessary to initiate disease modifying treatments earlier, before the onset of clinical dementia (Aisen, et al., 2010). It is possible that this consideration explains the failure of the humanized monoclonal antibody bapineuzumab (which targeted brain amyloid) to demonstrate clinical efficacy in late-phase studies in mild-to-moderate AD dementia.

The primary patient population of focus in this study is subjects with MCI/Prodromal AD and they will be recruited during both Stage A and Stage B of the study. The mechanism of action of a BACE1 inhibitor where amyloid production is reduced means E2609 is more likely to be efficacious (ie, slow disease progression) the earlier in disease progression treatment is started, where limited neurodegeneration has occurred and associated clinical deficits are at a minimum. Key safety aspects will be assessed in Stage A in which the MCI/Prodromal AD subjects have less advanced disease compared with subjects with mild AD who will also be recruited in Stage B.

As discussed, efficacy is more likely to be observed in subjects with MCI/Prodromal AD but there is the possibility that efficacy will also be evident following administration of an amyloid modifying agents such as E2609 in subjects with slightly more advanced disease such as mild AD. A study of tarenflurbil, a selective Aβ(1-42)-lowering agent, on cognition and function in subjects with mild to moderate AD showed only the subjects with mild AD had lower rates of decline than those in the placebo group in activities of daily living and global function; however, slowing of cognitive decline did not differ significantly (Wilcock, et al., 2008). Similarly, differential effects on cognitive measures have been observed with solanezumab, where some benefit from treatment was observed in subjects with mild AD but not in subjects with moderate AD, although studies with solanezumab were considered to have failed to improve cognition or functional ability significantly (Doody, et al., 2014). Therefore, it is relevant to compare the effect of the BACE1 inhibitor E2609 in 2 different subject populations that differ in terms of AD severity before the initiation of large Phase 3 clinical studies.

### 9.2.3 Rationale for the Use of Bayesian Adaptive Design

This study uses a Bayesian adaptive design for the MCI/Prodromal cohort only in Stage B. This design optimizes subject allocation and evaluation of efficacy in a smaller number of subjects by maximizing the number of subjects exposed to doses of interest. Frequent interim analyses will be performed to assess the probability of early success and futility and to aid in making early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis, such that subjects are more likely to receive a dose that is efficacious.

Subjects with mild AD recruited in Stage B will be assessed as a "nested" population that does not follow the Bayesian adaptive design. It was not considered appropriate to have a Bayesian design for both cohorts as this would have substantially increased the overall study sample size, delayed analyses of dose response, and would have added background "noise" for the comparison of subjects with MCI/Prodromal AD compared with those with mild AD. Data from each cohort will be analyzed independently for the purposes of decision making. A separate analysis of the 2 cohorts avoids the risk of data from subjects with mild AD confounding the results for the primary population (MCI/prodromal).

### 9.2.4 Rationale for Clinical Endpoints

The ADCOMS (Hendrix, et al., 2012) was developed utilizing data from multiple studies to investigate responsiveness to progression and treatment effects rather than sensitivity to baseline deficits. The score was built empirically with no a priori assumptions, using a partial least squares regression model for placebo data from 4 MCI studies with a duration $\geq$12 months. A combination of cognitive and functional items was selected from a variety of well-established and validated scales that is most sensitive to change over time. The partial least squares regression coefficients from the model were used to form a weighted composite score comprising a total of 12 individual items taken from the ADAS-cog (4 items), the MMSE (2 items), and CDR (6 items), that assess both cognition and global function. Performance of the ADCOMS has been assessed against the original scales in several studies.

The use of the ADCOMS allows for substantial sample size reductions in non-enriched and enriched MCI populations even over a 12-month period by increasing sensitivity. This derived score has shown adequate sensitivity in the MCI due to AD amyloid confirmed (CSF Aβ-positive) subgroup.

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007).

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The CDR is a clinical global rating scale requiring the interviewing of both the subject and an informant who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The CBB is a brief, computer-administered cognitive test battery that requires approximately 10 minutes for administration (Darby, et al., 2012; Fredrickson, et al., 2008; Maruff, et al., 2009). The CBB has been used to detect cognitive impairment in several neurodegenerative conditions including the measurement of cognitive function in healthy older adults and in adults with clinically diagnosed AD and prodromal AD (Darby, et al., 2009; Hammers, et al., 2012; Lim, et al., 2012a; Lim, et al., 2012b). The administration, scoring, and reporting of the CBB is automated and highly standardized, resulting in cognitive paradigms that have been well-validated in neuropsychological and cognitive studies (Fredrickson, et al., 2008; Maruff, et al., 2009). See Section 9.5.1.3.1 for further details.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al,. 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials on the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson et al., 2011, Lim, et al., 2012a, Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with E2609 treatment.

Volumetric magnetic resonance imaging is discussed in Section 9.2.5.4.

### 9.2.5 Rationale for Biomarkers

#### 9.2.5.1 Overall Rationale

The biomarker strategy for this study includes the following aims:

- To establish an amyloid load in the brain at study entry (via the PET eligibility inclusion criterion)
- To evaluate safety (principally by magnetic resonance imaging [MRI])
- To confirm a PD effect in terms of both Aβ in CSF and brain amyloid assessed by PET and to establish that this PD effect is maintained long-term
- To evaluate disease modification through longitudinal assessments of vMRI, amyloid PET, and CSF biomarkers of neurodegeneration (tau and p-tau)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

#### 9.2.5.2 Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect of E2609 on Aβ(1-40) +Aβ(1-42) and other C-terminally truncated Aβ peptides such as Aβ(1-38) through inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using $^{[11}$C$^{]}$PiB, suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases in CSF Aβ concentrations that are seen in AD are believed to be related to this decrease in brain Aβ availability.

Both total tau (t-tau) and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni and Bhaskar, 2012). CSF tau measurements have been correlated with cerebral atrophy, while their ratios with Aβ42 have provided useful predictors of cognitive decline and progression to dementia due to AD. Rebalancing dysregulated amyloid production early in the process may positively affect the neurodegenerative process and thus affect these markers and benefit the disease trajectory. Therefore, monitoring these markers in conjunction with amyloid imaging may provide further supportive evidence of efficacy.

Baseline levels of Aβ(1-42), tau, and p-tau will also help elucidate the extent of AD pathology at entry to the study and can be combined with baseline levels of *ApoE4* genotyping in addition to the baseline imaging variables to help explain differences in treatment response.

The study will be stratified at randomization for *ApoE4* gene status in order to account for any *ApoE* status by treatment interaction or *ApoE* status by amyloid-related imaging abnormalities risk interaction.

#### 9.2.5.3 Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) to confirm the presence of AD pathology in the brain of subjects with MCI/Prodromal AD or mild AD at entry to the study; and 2) to evaluate the effects of E2609 on amyloid levels in the brain, both by whole brain analysis (the average of 5 to 6 cortical regions) and brain region analysis.

Longitudinal amyloid PET imaging will be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug) as an exploratory measure of the potential disease-modifying effects of E2609. Longitudinal amyloid PET imaging will only be conducted until 18-month PET scans of acceptable quality have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used.

#### 9.2.5.4 vMRI

Volumetric imaging will be used to evaluate the effects of E2609 on rates of atrophy across the different dose groups and to provide support that effective treatment is associated with modification of disease course (secondary endpoint for the MCI/Prodromal population and exploratory endpoint for the Mild AD population). A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. Clinically efficacious doses are predicted to be associated with a slowing in the rate of hippocampal atrophy compared with rates observed in the placebo and non-efficacious dose groups. Treatment effects on left and right hippocampal, whole brain, and total ventricular volumes are exploratory endpoints.

Annualized rates of change of 2% to 3% have been reported for the AD brain compared with 1% in MCI and <1% in age-matched controls (Hua, et al., 2010, Leung, et al., 2010). However, subjects with MCI due to AD-dementia (CSF Aβ <192 pg/ml or positive amyloid imaging) show rates of atrophy comparable to those observed in subjects with AD-dementia (Hua, et al., 2009; Hua, et al., 2010; Leung, et al., 2010; Morra, et al., 2009), supporting the notion that such subjects are on similar trajectories as mild AD-dementia. Lower levels of CSF Aβ42, amyloid positivity on PET imaging, and higher levels of CSF tau in addition to the presence of the *ApoE4* allele have all been associated with greater rates of brain atrophy (Fjell, et al., 2010a; Fjell, et al., 2010b) and will be entered as covariates in various analyses. Hippocampal atrophy has also been shown to predict clinical progression independently of amyloid levels in the brain (Jack, et al., 2010), and this measure will be entered as a covariate in the analysis of the clinical endpoints along with the aforementioned variables.

Brain volume (total ventricular volume, whole brain, temporal lobe) generally shows a modest correlation with performance on a number of cognitive scales (Hua, et al., 2009; Hua, et al., 2010; Freeborough, et al., 1997; Leung, et al., 2010). Using volumetric analysis performed at 6-month intervals, these relationships and the effects of E2609 treatment will be explored further. Recent advances in analysis software have made structural imaging more sensitive to detect small changes and able to reliably measure rates of atrophy at these intervals, particularly in the posterior parietal and the lateral temporal regions during the early stages of disease (Hua, et al., 2009; Hua, et al., 2010). Given these observations, a demonstration of significant slowing or stabilization in the rate of atrophy in response to treatment, compared with placebo, will offer further support for disease modification.

### 9.2.6 Clinical Risks and Mitigation Strategy

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, and to mitigate clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. These safety aspects include the following:

- Two-stage study design: there will be a pause in recruitment after 60 MCI/Prodromal subjects have been randomized to study drug (Stage A). Only after the safety of E2609 in these first 60 subjects (consisting of at least 12 weeks data for the latter subjects and longer dosing periods for the earlier subjects) has been reviewed by the DSMB and considered acceptable, will randomization of further subjects into the study commence (Stage B).
- Immunology-related and infection-related exclusion criteria
- Review of unblinded safety data by an independent DSMB at regular intervals
- Safety withdrawal criteria based on CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cell) and other lymphocytes (absolute counts and percentage change from baseline), skin rash, reoccurrence of herpes virus infections including any oral herpes, genital herpes or shingles, other infections, MRI changes, ECGs, and pregnancy.

In addition to the features above, other safety aspects of this study designed to mitigate clinical risk include the following:

- Blinded safety data will be monitored by Eisai at regular intervals during the course of the study
- Routine safety assessments will include the monitoring and recording of all AEs and SAEs, monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular ECGs, physical and neurological examinations, and dermatological assessments at regular intervals. Information for AEs relating to abuse potential will be collected via a detailed narrative. Subjects reporting AEs relating to abnormal dreams or sleep-related events, or sleep terror will be questioned on the frequency and impact of these events.

- As per the communication from the Food and Drug Administration (FDA) in Aug 2013, there are concerns that hypopigmentation of the skin and mucous membranes may occur with BACE1 inhibitory drugs. Although no such effects have been seen with E2609 to date, assessments by a dermatologist will be performed at regular intervals during the study. These assessments will specifically include evaluation of any areas of depigmentation or any rash. Dermatological assessments will be supplemented with a specific question to subjects regarding skin changes at each visit. Any such changes could be referred to the dermatologist for further evaluation. See Section 9.5.1.5.8 for further details.
- Baseline and on-study blood, DNA, and CSF samples will be taken and stored for all subjects. These samples may be tested in the event that a subject develops AEs that warrant further investigation (eg, if a subject develops a treatment-emergent infection) (see Section 9.5.1.2.3).
- Central reading of safety brain MRI assessments (including any MRI evidence of demyelination) will be performed at Screening, at approximately 6-month intervals during the Treatment Phase of the study, and at the final Follow-Up Visit.
- Full neurological examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations. Details of the neurological examination are given in Section 9.5.1.5.9.
- Cognitive decline will be assessed as a safety assessment (ADAS-cog$_{14}$, MMSE, and CBB). Of particular importance will be the assessment of reaction time testing using the detection and identification tasks on the CBB.
- An assessment of suicidality using the C-SSRS will be performed at Screening, Baseline, and at regular intervals during the Treatment Phase and Follow-Up periods of the study (see Section 9.5.1.5.11).
- All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will have at least 2 off-treatment Follow-Up visits (4 and 12 weeks after the last dose of study drug). More frequent safety assessments can be made as unscheduled assessments/visits during the off-treatment Follow-Up period, if clinically indicated.
- An ophthalmic examination will be conducted at Baseline and if the subject experiences visual disturbances during the course of the study (see Section 9.5.1.2.1).

## 9.3 Selection of Study Population

Stage A will enroll 60 eligible MCI/Prodromal subjects at 25 centers in the United States. Stage B will enroll up to an additional 440 eligible MCI/Prodromal subjects at approximately 125 centers globally; the final total number will depend upon whether the prespecified criteria for either early success or futility are met. In addition, a separate cohort of approximately 200 mild AD subjects will be randomized and dosed during Stage B.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

### 9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Meets the core clinical research criteria of the NIA-AA for MCI due to AD (Albert, et al., 2011) or AD dementia (McKhann, et al., 2011) and is "staged" or classified as either MCI (Stage A and Stage B) or mild dementia (Stage B only) and also complies with the following:

**Required at both Screening and Baseline:**

   a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician's observation
   b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT
   c. FAQ ≤20
   d. MMSE ≥20
2. Amyloid positive PET image based on centralized PET scan reading
3. Males and females aged 50 to 85 years, inclusive at time of consent
4. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant need not be living in the same residence as the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At visits where the CDR or FAQ are conducted, caregivers or informants need to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator will determine whether attendance in person is required or whether telephone contact will be suitable and will base this determination upon the functional ability of the subject among other factors.
5. Subjects who are receiving acetylcholinesterase inhibitor (AChEIs) or memantine must be on a stable dose for at least 12 weeks before the Baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.

6. Subjects must have been on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization
7. Females must not be lactating or pregnant (as documented by a negative beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) at Screening or Baseline. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
8. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception other than hormonal contraceptives (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. If currently abstinent, the subject must agree to use a double barrier method as described above if she becomes sexually active during the study period or for 30 days after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for ≥12 consecutive months, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (ie bilateral tubal ligation, total hysterectomy or bilateral oophorectomy, all with surgery ≥1 month before dosing).
9. Male subjects must have had a successful vasectomy (confirmed azoospermia) or they and their female partners must meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period and for 30 days after study drug discontinuation). No sperm donation is allowed during the study period and for 30 days after study drug discontinuation.
10. Provide written informed consent
11. Willing and able to comply with all aspects of the protocol

### 9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD pathology, including any co-morbidities detected by neurological examination or MRI
2. Modified Hachinski Ischemic Scale >4
3. History of transient ischemic attacks or stroke within 12 months of Screening

4. A history of epilepsy. Subjects with a history of seizures (not including a history of simple febrile seizures in childhood) within 10 years of Screening. Subjects with disturbance likely to be due to seizures within 5 years of Screening.
5. Significant pathological findings on the brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter), any microhemorrhage which is symptomatic, a single macrohemorrhage greater than 10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic edema, greater than 3 lacunar infarcts or a single infarct >2 cubic centimeters involving a major vascular territory, evidence of severe microangiopathy, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions or space-occupying lesions (eg, arachnoid cysts) or brain tumors (eg, meningioma).
6. Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that could confound the MCI/Prodromal or mild AD diagnosis or could interfere with study assessments or procedures
7. A score of ≥8 on the 15-item Geriatric Depression Scale (GDS) at Screening
8. Abnormally low serum vitamin B12 levels for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the LLN for the testing laboratory)
9. Thyroid stimulating hormone above the normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects regardless of whether or not they are taking thyroid supplements.
10. Any contraindications to MRI or PET scanning, including cardiac pacemaker/ defibrillator or ferromagnetic metal implants (eg, in skull; cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded.
11. Any contraindications to lumbar puncture (LP) for CSF sampling (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, including but not limited to obesity)
12. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
13. History of Ig deficiency or other immunodeficiency disorders (including subjects known to be human immunodeficiency virus positive)
14. Subjects with chronic viral hepatitis
15. A history of tuberculosis (TB). Subjects with no history of TB will be tested for previous TB exposure (eg, positive tuberculin skin test, interferon gamma release assay or other locally accepted tests) and a positive test will be exclusionary.
16. A history of ophthalmic shingles
17. A history of ocular herpes simplex virus (HSV) infection
18. Any live vaccine in the 3 months before randomization.
19. Any active infection within the last 4 weeks prior to randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve; psychometric tests conducted at Visit 2 (eg, MMSE, CDR, etc) must be repeated.

20. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy. Subjects with:
    a. Seasonal or perennial allergic rhinitis, asthma or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids need not be excluded.
    b. Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy need not be excluded.
    c. Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy need not be excluded (topical steroid treatment is permitted).
21. CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below LLN and confirmed by a repeat test conducted 1 week after the initial test
22. Ig (IgG, IgA, or IgM) levels below the LLN
23. Clinically significant deviation from normal in physical examination, vital signs, or clinically laboratory tests at Screening or Baseline
24. A prolonged QT/ corrected QT interval (QTc) interval (QTc >450 msec) at Screening or Baseline as demonstrated by average QTc interval from triplicate ECGs. A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolong the QT/QTc interval.
25. Any other abnormality of the ECG at Screening or Baseline (including QRS >110 msec, abnormal electrical axis, PR interval >220 msec and conduction abnormalities) considered clinically significant by the investigator
26. Left bundle branch block at Screening or Baseline
27. Persistent heart rate <50 or >100 beats per minute (bpm) at Screening or Baseline
28. Persistent systolic blood pressure (BP) >165 mmHg or <90 mmHg and diastolic BP >100 mmHg or <60 mmHg at Screening
29. History of cardiac arrhythmias. Subjects with other heart diseases (eg, ischemic heart disease, clinically significant valvular heart disease) that are not stably and adequately controlled, or uncompensated heart failure (New York Heart Association Class III and Class IV)
30. Type 1 or Type 2 diabetes mellitus that is not well controlled
31. Malignant neoplasms within 5 years before Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer that did not require systemic therapy; these do not exclude the subject). Subjects who had malignant neoplasms but who have had at least 5 years of documented evidence of no active disease before Screening need not be excluded.
32. Medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) that are not stably controlled, or which, in the opinion of the investigator(s), could affect the subject's safety or interfere with the study assessments
33. Hypopigmentation conditions (eg, albinism and vitiligo)

34. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive for benzodiazepines or opioids in the urine drug screen need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications containing benzodiazepines or opioids for a medical condition that is not exclusionary and not due to drug abuse.
35. Has a "yes" answer to the C-SSRS suicidal ideation questions 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit; or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
36. Violations of the medical restrictions as specified in the Concomitant Medications section of the protocol
37. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
38. Participation in any other interventional clinical study related to cognitive impairment within 6 months before Screening unless it can be documented that the subject was in a placebo treatment arm
39. Currently enrolled in another clinical study or used any investigational drug or device within 60 days or 5 half-lives of the investigational medication (whichever is longer) preceding informed consent
40. Hypersensitivity to the study drug or any of the excipients or to other BACE inhibitors, or to the PET tracer, or components of its formulation

### 9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). Follow-Up Visits will also be scheduled 4 and 12 weeks after the last dose of study drug (see Section 9.1.2.3). Subjects who discontinue study drug prematurely will also be scheduled to return to the study site to undertake limited efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, CBB, and ISLT) at Week 53 (Visit 16) and Week 79 (Visit 18), if these 2 visits have not already been performed.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the Subject Disposition eCRF page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug

Dosing eCRF page. If a subject discontinues study drug and withdraws from the study at the same time, the ED Visit will be followed (see Section 9.5.5).

Safety-related withdrawal criteria for the study will include the following:

a. A withdrawal threshold will be set based on absolute counts of CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells). The withdrawal threshold will be set at below the level of the LLN, at a level that represents a greater risk of opportunistic infection in the treated population. For CD4 (T helper cells) the withdrawal threshold is 250 cells/µL. For CD8 (cytotoxic T cells) and CD19 (B cells) the withdrawal thresholds are 150 cells/µL and 50 cells/µL, respectively. Any subject who has CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below the withdrawal threshold as confirmed by a repeat test conducted within 1 week of the initial test will be withdrawn from the study.
b. Subjects with CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between the LLN and the withdrawal threshold will have lymphocyte subset counts performed on a weekly basis. Subjects with a >33% reduction from baseline in CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts will also have lymphocyte subset counts performed on a weekly basis. For these subjects, the decision as to whether the subject remains in the study or is to be withdrawn from the study will be based upon clinical judgment and will take into account any clinical presentation in addition to the lymphocyte subset counts. These subjects may continue with treatment if there is no clinical evidence of infection. They will be discontinued from study drug if they have infections of a moderate to severe intensity (eg, subjects whose infections are not localized, or are systemically unwell, or who require systemic antiinfective drug treatment).

**Table 1 Study Conduct Actions for Lymphocyte Subset Absolute Counts**

| Lymphocyte subset absolute counts | Action | Continue in or withdraw from study? |
|---|---|---|
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below withdrawal threshold | Retest within 1 week | If retest performed within 1 week confirms lymphocyte subset counts below the withdrawal threshold, subject to be withdrawn from study |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between LLN and withdrawal threshold or >33% reduction from baseline in CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts | Lymphocyte subset counts to be performed weekly until counts return to ≥ LLN or no more than 33% reduction from baseline | Decision will be based upon lymphocyte subset counts and clinical judgment |

LLN = lower limit of normal.

c. Subjects with clinical evidence of infection will have their CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts measured. Blood and other biological samples will also be collected for investigations of infective pathogens (eg, serological tests, quantitative polymerase chain reaction, microscopy, and culture) where appropriate. In subjects with infection, if any of their absolute cell counts meets the withdrawal thresholds, study drug will be discontinued. All subjects with severe infections will be withdrawn. All subjects with herpes zoster (shingles) or ocular herpes infections will be withdrawn, regardless of severity of presentation. Subjects with mild or moderate infection may continue treatment with study drug unless otherwise clinically indicated or otherwise specified below. Specifically, when any of the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts are between the LLN and the withdrawal thresholds or have shown >33% reduction from baseline, subjects with infections of moderate intensity will be discontinued from study drug (eg, subjects whose infections are not localized, or subjects who are systemically unwell, or who require systemic antiinfective drug treatment). All subjects with infection who are withdrawn will be followed for a period of 12 weeks or until the infection resolves/ stabilizes or until the CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) absolute counts have returned to >LLN (whichever comes latest).

**Table 2 Study Conduct Actions for Lymphocyte Subset Absolute Counts and Infection**

| Criterion | Severity of Infection | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts below withdrawal threshold | Withdraw | Withdraw | Withdraw |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts between LLN and withdrawal threshold or >33% reduction from baseline in CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts | May continue treatment with study drug unless clinically indicated | Withdraw | Withdraw |
| CD4 (T helper cells), CD8 (cytotoxic T cells), or CD19 (B cells) absolute counts always >LLN and no reduction from baseline >33% | May continue treatment with study drug unless clinically indicated | May continue treatment with study drug unless clinically indicated (See (e) for exception) | Withdraw |

LLN = lower limit of normal.

d. A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (see (e) for exception), will be discontinued from study drug and a dermatological consult will be requested regardless of whether the rash is considered drug-related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatological consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

e. Subjects who develop moderate to severe oral or genital herpes should be withdrawn from the study. Subjects who develop a mild case of oral or genital herpes may remain in the study even if the event lasts more than 72 hours.

f. Development of any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. If discontinued from study drug, subjects will undergo an ED Visit within 7 days after discontinuation and will attend the Follow-Up Visits 4 and 12 weeks after the last dose of study drug. They will also undertake an Unscheduled Visit (with MRI) at approximately 4 weeks after the visit at which such MRI features were first identified. An MRI will also be performed at approximately the time of the second Follow-Up Visit (Visit 20). Additional visits for safety may be arranged if clinically indicated in the opinion of the investigator, including after 12 weeks after the last dose of study drug. At any time during the treatment period, subjects who have asymptomatic, treatment-emergent microhemorrhages found on MRI, but none of the features which merit discontinuation of treatment (ie, vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic treatment-emergent microhemorrhage) may continue with treatment. These subjects will have safety assessments (including MRI) at approximately 4 weeks after the visit at which such MRI features were found. They will also continue with the scheduled MRI scans. Additional unscheduled MRI scans may be arranged on an individual subject basis in discussion with the study medical monitor.

g. A postdose ECG with an average QTcF interval >500 msec from triplicate ECGs

h. A postdose ECG with a QTcF interval increase from baseline >60 msec and a QTcF interval >450 msec as demonstrated from triplicate ECGs

i. Any seizure (motor or non-motor)

j. Pregnancy

## 9.4 Treatments

### 9.4.1 Treatments Administered

For this study the test drug is E2609 and the control drug is placebo. All study drugs are to be administered orally, QD, with food. As shown in Figure 1, there will be 4 treatment arms in the MCI/Prodromal Cohort where E2609 will be administered at 3 doses (5 mg, 15 mg and 50 mg) and the comparator is placebo. In the Mild AD Cohort, there will be 3 treatment arms where E2609 will be administered at 2 doses, and the comparator is placebo. The 2 highest E2609 doses (15 mg and 50 mg) taken into Stage B, after the PK/PD and safety review from Stage A for the MCI/Prodromal group, will be used for the Mild AD population.

Study treatment will begin on Day 1 (at the study site) following Randomization and will continue for approximately 78 weeks. Please refer to Table 7 and Section 9.5.1.4.1 for specific information on drug administration on days when PK sampling is to be performed.

Study drug doses will remain the same for each individual subject unless the interim PK/PD analysis determines that an entire dose level requires adjustment (Section 9.4.4). See

Section 9.3.3 for safety related withdrawal criteria for the study. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

### 9.4.2 Identity of Investigational Product

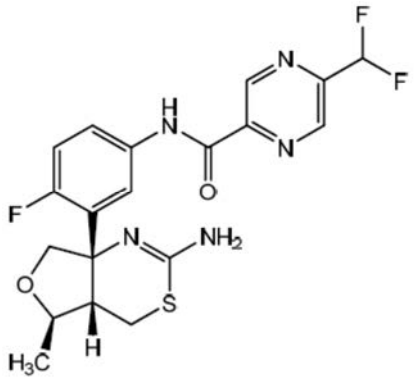
E2609 tablets of 5-mg, 10-mg and 25-mg dose strengths will be supplied. Placebo tablets of identical appearance will also be available. Each subject will receive 2 tablets, which combined will make up the required doses of E2609 5 mg, E2609 15 mg, E2609 50 mg, or placebo. The tablets will be supplied by the Sponsor in labeled blister packs. The product release certificates for E2609 and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either E2609 or placebo, or both (see Section 9.4.2.3 for labeling details).

#### 9.4.2.1 Chemical Name, Structural Formula of E2609

- Test drug code: E2609
- Generic name: not applicable
- Chemical name: International Union of Pure and Applied Chemistry
- *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44
- Structural formula:



#### 9.4.2.2 Comparator Drug

Not applicable.

#### 9.4.2.3 Labeling for Study Drug

E2609 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier (ID)
- Lot number/batch number
- Storage conditions, expiration date if necessary

#### 9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

### 9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used for MCI/Prodromal subjects and for mild AD subjects are described in Section 9.4.1.

Randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized blister card identification numbers. At enrollment, the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 3), the IxRS will assign each subject a unique randomization number.

### 9.4.4 Selection of Doses in the Study

It is not known how the level of CSF or brain Aβ reduction is related to clinical efficacy. Therefore, in this study, doses will be selected such that at steady state, they will result in 25%, 50%, and 75% reduction in CSF Aβ levels from baseline to cover a broad range of PD effects.

In Study 007, the relative bioavailability of a tablet formulation of E2609 in the fed and the fasted states compared with the capsule formulation in the fasted state (used in Studies 001 and 002) was investigated. It was found that when the tablet form of E2609 (50 mg) was administered with food, the exposure (ie, AUC) of the parent drug E2609 was higher, with lower maximum observed concentrations and reduced exposure to the metabolites, compared with either formulation in the fasted state.

Based on the PK/PD modeling using data from healthy volunteer Studies 001, 002, and 007, doses of 5 mg, 15 mg, and 50 mg QD administered as the tablet formulation with food in this study should achieve CSF Aβ reduction from baseline of approximately 25%, 50%, and 75% at steady state, respectively (Table 3).

**Table 3 Predicted Steady State Plasma PK Parameters and CSF Amyloid β Reduction From Baseline**

| E2609 Tablet Daily Dose (mg) With Food | E2609 Plasma $C_{max,ss}$ (ng/ml) | E2609 Plasma $C_{ss,av}$ (ng/ml) | E2609 Plasma $AUC_{(0\text{-}24h)ss}$ (ng.h/ml) | % Reduction CSF BACE1 Activity | % Reduction CSF Aβ(1-x) |
|---|---|---|---|---|---|
| 5 | 6.2 | 3.3 | 80.3 | 16.2 | 33 |
| 15 | 18.6 | 10 | 240.9 | 36.6 | 56 |
| 50 | 62.1 | 33.5 | 803.0 | 65.7 | 79 |

Aβ(1-x) = amyloid beta monomer from amino acid 1 to x, $AUC_{(0\text{-}24h)ss}$ = area under the concentration x time curve at steady state from time zero to 24 hours, BACE1 = Beta-amyloid converting enzyme, CSF = cerebrospinal fluid, $C_{ss,av}$ = average steady-state concentration, $C_{max,ss}$ = maximum plasma concentration at steady state, PK = pharmacokinetics.

The PK/PD modeling described above, which was conducted using data obtained from healthy volunteers, has also been supported by modeling of data from subjects with an underlying AD pathology (Study 101). Furthermore, external data with another BACE1 inhibitor (MK-8931) showed a similar PD effect in AD patients as in healthy volunteers (Forman, et al., 2013). Therefore we are confident that the modeling of E2609 effects in healthy subjects will be applicable for both MCI/Prodromal and Mild AD dementia patients.

The exposure of the highest dose in this study (50 mg QD tablet administered with food) is less than that of the 100 mg QD dose (capsule administered fasted) in Study 002.

The 100 mg QD dose administered for 14 days in Study 002 was well tolerated with no clinically significant changes in laboratory parameters, vital signs, or ECG parameters. On Day 15, for the 100 mg QD cohort in Study 002, there was a reduction of CD4

lymphocyte counts compared with placebo (CD4 lymphocyte counts on E2609 decreased by 3.1% from baseline, whereas the placebo control showed an increase of 8.7%), but this decrease was less than that observed at doses of 200 mg (22.9% decrease) or 400 mg (17.3% decrease). No subjects had infections or drug rash while receiving E2609 100 mg QD or at lower doses in Study 002, whereas at 200 mg and 400 mg QD, 4 subjects had symptomatic orolabial HSV1 relapses and 2 subjects at the highest dose had drug rash. The highest dose for Study 202 of 50 mg QD (tablet administered with food) is therefore expected to have a similar or better safety profile compared with the 100 mg QD capsule (administered fasted) in Study 002. Specific exclusion criteria, blinded and unblinded safety monitoring procedures, and safety withdrawal criteria are included in this study in order to mitigate any immunology-related risk with E2609, particularly in light of the progression from 14 days of dosing (Study 002) to 18 months of dosing in this study.

Subjects in the MCI/Prodromal cohort, whether in Stage A or Stage B, will be randomized to receive either placebo or E2609 at 5 mg, 15 mg, or 50 mg QD. Subjects with mild AD (Stage B) will be randomized to receive either placebo or E2609 at 15 mg or 50 mg QD, but not the 5-mg QD dose. The rationale for not including an E2609 5-mg QD dose in the dose regimens for subjects with mild AD is that more advanced disease may require greater reduction in CSF Aβ levels for comparable effects.

After 60 MCI/Prodromal subjects in Stage A have completed 4 weeks of treatment, an interim analysis of the E2609 PK and PD profiles will be used to confirm the E2609 doses to be used for Stage B, where PD is measured as reductions from baseline in CSF Aβ(1-x) levels. If the 95% confidence interval of the mean percentage change from baseline in CSF Aβ(1-x) measured after 4 weeks of treatment with a dose of E2609 does not include its intended target value (ie, 25%, 50%, and 75% reductions from baseline, respectively for E2609 at 5 mg, 15 mg, and 50 mg), PK/PD modeling will be conducted. This PK/PD modeling will use the observed PK and PD data from Stage A and will relate the average steady state plasma concentration of E2609 to steady state CSF Aβ(1-x) percentage reduction from baseline after 4 weeks of dosing. From this model, the new target plasma steady state concentrations of E2609 required to achieve the target levels of CSF Aβ(1-x) reduction will be estimated again. Dose adjustment for Stage B may be considered if it is possible to get closer to the new target plasma steady state concentrations of E2609 required to achieve the intended target levels of CSF Aβ(1-x) reduction than is possible with the initially planned doses, given the limitation that E2609 dose adjustments will have to be in 5-mg increments or decrements. Subjects already randomized to a dose that needs to be adjusted will be switched to the new adjusted dose and complete their treatment at this new dose.

If dose adjustment is required for Stage B, a protocol amendment reflecting the new doses will be submitted.

### 9.4.5 Selection and Timing of Dose for Each Subject

E2609 is administered orally, QD, with food. Study treatment will begin on Day 1 following randomization and will continue for approximately 78 weeks.

### 9.4.6 Blinding

E2609 and placebo will be administered as tablets of identical appearance.

During the Randomization Phase and Follow-Up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and Eisai staff will be blinded to the treatment codes (double-blind).

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments (ie, those who are trained and certified to perform the various cognitive assessments that are undertaken in this study). Furthermore, at the site, the notes and reports relating to safety assessments must be kept separate from the notes and reports relating to efficacy.

Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

At the end of Stage A, PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether E2609 exposure and PD effects are similar between MCI/Prodromal subjects in Stage A of the present study and healthy subjects in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

At the conclusion of the study, all unused drug supplies are to be returned to the Eisai approved contract packaging vendor.

### 9.4.7 Prior and Concomitant Therapy

Medication (including over-the-counter medications) or therapy administered to the subject before the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, Listing 3, Listing 4, and Listing 5. Medications that are permitted with restrictions are listed in Listing 6, Listing 7, and Listing 8).

The following agents are not permitted before randomization (specific timeframes are shown below) and throughout the study until after the last treatment visit:

- Anticoagulants (eg, warfarin, digabatrin) are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization
- Drugs which may cause QTc prolongation are not permitted for a period of 5 half-lives or 14 days (whichever is longer) before randomization
- Live vaccines are not permitted within 3 months before randomization. This does not apply to non-live/inactivated vaccines
- Ig therapy and biologic drugs are not permitted within 6 months before randomization
- Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization

Subjects taking AChEIs or memantine must meet the following criteria in order to be included in the primary analyses:

- On a stable dose for 12 weeks before the Baseline cognitive assessments at Visit 2
- Remain on a stable dose while on study

Subjects who initiate treatment with an AChEI or memantine during the study, or who change their dose of AChEI or memantine while on study, will be allowed to continue in the study, but their clinical efficacy data will be censored from the time of drug initiation for the primary analyses.

Subjects taking all other non-prohibited concomitant medications must meet the following requirements:

- Must be on stable dose for at least 4 weeks before randomization, except for medications that are administered as short courses of treatment or which are to be used intermittently as needed
- Medications that are used as needed, rather than on a stable daily basis, and which are central nervous system (CNS) active and may affect cognitive function, are not permitted during a period of 72 hours before cognitive testing

Subjects who initiate treatment with or have dose adjustment of drugs not intended for treatment of cognitive impairment during the study may continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety, and

are not prohibited above. If the subject initiates treatment for co-morbidities with a (non-prohibited) drug that may affect cognitive function, the subject should not have cognitive assessments performed until the dose has been stable for at least 4 weeks.

### 9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Phase of the study. CRAs will review treatment compliance during site visits and at the completion of the study.

### 9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the principal investigator including a copy of the principal investigator's current medical license (required for United States sites) or medical registration number on the curriculum vitae
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

## 9.5 Study Assessments

### 9.5.1 Assessments

#### 9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

#### 9.5.1.2 Baseline Assessments

Assessments to be made at Screening and Baseline and throughout the study are described in Section 9.5.1.3, Section 9.5.1.4, and Section 9.5.1.5.

##### 9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, current medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment due to AD. Subjects will be asked about history of TB, infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV Types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include onset, duration, relapse frequency, severity, and treatments. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The 15-item GDS and modified Hachinski ischemic scale will also be assessed at Screening as part of the exclusion criteria.

Physical examinations (complete or routine) will be performed as designated in Table 6. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, and skin, and a neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

An ophthalmic examination will be conducted at Baseline. If the subject experiences visual disturbances during the course of the study, the subject will be referred to a specialist for a further ophthalmic examination including a retinal examination.

Additionally, at the Screening Visit, inclusion and exclusion criteria and prior medications will be reviewed with the subject and caregiver or informant, and a serum β-hCG pregnancy test (females of childbearing potential only) will be conducted. Blood will also be collected for chemistry and hematology tests, thyroid function tests, lymphocyte subsets analysis,

Ig levels, viral screening (for hepatitis B surface antigen and hepatitis C antibodies), vitamin B12, and a test for previous TB exposure. Urine will be collected for urinalysis and drug screening.

Height will also be measured.

#### 9.5.1.2.2 PSYCHOMETRIC ASSESSMENTS

The MMSE, CDR, FAQ, ISLT, and the CBB will be administered at Screening and Baseline to determine eligibility. See Section 9.5.1.3.1 for further details. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws).

#### 9.5.1.2.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

**Biomarkers**

Subjects will be encouraged to stay at the site after completion of LP for medical observation. At Baseline, CSF will be collected by LP after fasting (preferred), or at least 2 hours after the most recent meal. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 and Visit 18) can be performed 4 and 8 hours postdose and at a similar time of day (±1 hour) for each individual subject. At visits where cognitive tests are also performed, the LP must be performed after the cognitive tests have been completed; the subjects should rest and drink some fluid to hydrate after the cognitive tests and before the LP. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. The CSF sample will be used for PD assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), t-tau, p-tau, and BACE. Aβ(1-x) in both CSF and plasma will be measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and post-screening analysis of CSF Aβ(1-42), t-tau, and p tau will be performed using ELISAs. BACE1 levels will be measured using internally developed fluorescence resonance energy transfer and ELISA based assay(s). Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

The blood sample collected for PD analyses at Baseline should be collected shortly after completing the LP at Baseline. The sample should be collected at fasting or at least 2 hours after the most recent meal.

At the Baseline Visit, CSF and blood samples will be collected and stored for determination of prior exposure to any suspected infective agents in the event that the subject develops treatment-emergent AEs that warrant further investigation (eg, treatment-emergent infection). Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by quantitative polymerase chain reaction, or human leukocyte antigen genotyping.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the samples.

**Amyloid PET**

Screening amyloid PET data will serve as the baseline data (Table 6). PET scanning will be performed with a locally approved Aβ imaging agent, eg, Amyvid. Descriptions and detailed instructions for all imaging can be found in the imaging manual.

**Pharmacogenetics**

A blood sample will be obtained at Baseline and will be used to determine the *ApoE* genotype (homozygous or heterozygous) and the *NAT2* phenotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response and safety.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

#### 9.5.1.3 Efficacy Assessments

##### 9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

The timing of psychometric assessments is shown in Table 6 and Table 7. These assessments should be administered in the morning (or, if not possible, consistently at the same time of day) and should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The order of assessments is: MMSE, CDR, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall) at Screening; and MMSE, CDR, ADAS-cog$_{14}$, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall) at the Baseline Visit.

At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

**The Derived Alzheimer's Disease Composite Score:** The primary efficacy endpoint is the change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects.

The ADCOMS is derived from the ADAS-cog (4 items), the MMSE (2 items), and the CDR (all 6 items), described below. The ADCOMS is more sensitive to clinical progression compared with currently existing clinical batteries and requires smaller sample sizes for clinical studies in MCI/Prodromal AD or mild AD. It also shows sensitivity to treatment

effects with AChEIs. The ADCOMS assesses both cognitive and functional domains and can be offered as a single primary clinical endpoint. The ADCOMS has a range from 0 to 1.97.

**CogState Brief Battery:** The CBB is a computer-based battery comprising 4 cognitive tests:

1. Detection – a simple reaction time test where the subject presses a key when the card is turned face up from a pack of cards ("Has the card turned over"). Speed of response is the measure.
2. Identification – a simple choice reaction time test where the subject presses 1 of 2 keys when the card just turned face up is either a red card or a black card ("Is the card red"). Speed of response is the measure.
3. One Card Back – a simple working memory test where the subject presses 1 of 2 keys when the card turned face up is either the card seen in the immediately previous trial or not ("Is the previous card the same"). Accuracy of response is the measure.
4. One Card Learning – a visual learning and memory test where the subject presses 1 of 2 keys depending on whether the card just turned face up has been seen before or not in the task ("Have you seen this card before in this task"). Accuracy of response is the measure.

**ISLT:** The ISLT is a verbal learning and memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 15 minutes, in which time the CBB is performed, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

**Mini Mental State Examination:** A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

**Clinical Dementia Rating:** The CDR assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

**Alzheimer's Disease Assessment Scale - cognitive subscale:** Discussed in Section 9.2.4.

**Functional Assessment Questionnaire:** Either a caregiver or informant or the subject provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

#### 9.5.1.3.2 VOLUMETRIC MRI

Volumetric MRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the Alzheimer's Disease Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

Volumetric MRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. Volumetric MRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. Volumetric MRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 6 and Table 7, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Descriptions and detailed instructions for all imaging can be found in an imaging manual that will be provided to the study sites.

#### 9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

CSF samples will be collected as specified in Table 6 and Table 7. The CSF sample taken at the Baseline Visit will only be performed after confirmation of an amyloid positive PET scan. See Section 9.5.1.2.3 for further details.

### 9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

#### 9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood and CSF samples will be collected for the determination of the concentrations of E2609. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with E2609.

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 6 and Table 7. Two PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visits 5, 11, 14, and 16, and 4 to 8 hours postdose at Visit 7 and Visit 18 (or at the ED Visit). Therefore,

subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or at the ED Visit) the PK blood sample should be collected shortly after completing the LP.

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

#### 9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

**Biomarkers**

Blood samples will be collected for PD assessments as specified in Table 6 and Table 7. See Section 9.5.1.2.3 for further details.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

**Amyloid PET**

An amyloid PET scan will be performed at Screening to confirm deposition of amyloid in the brain. Longitudinal amyloid PET imaging will also be conducted after 18 months of treatment (or at ED, providing the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted until acceptable 18-month PET scans have been obtained for at least 25 subjects per treatment arm for each amyloid PET ligand used (Table 6). PET scanning will be performed with a locally approved Aβ imaging agent, eg, Amyvid.

Amyloid PET imaging is an exploratory measure of the potential disease-modifying effects of E2609.

Descriptions and detailed instructions for all imaging can be found in the imaging manual.

### 9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, lymphocyte subsets, Igs, and urine values; periodic measurement of vital signs and ECGs; performance of physical and neurological examinations; dermatological assessments; the C-SSRS; and safety MRIs as detailed in Table 6 and Table 7.

Every effort should be made to keep the site staff responsible for reviewing laboratory reports and assessing AEs separate from the site staff responsible for the efficacy assessments (see Section 9.4.6).

#### 9.5.1.5.1 Adverse Events and Other Events of Interest

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E2609.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not

A laboratory result should be considered by the investigator to be an AE if it:

- Results in the discontinuation of study drug
- Results in withholding of study drug pending some investigational outcome
- Results in an intervention, based on medical evaluation (eg, potassium supplement for hypokalemia)
- Results in any out-of-range laboratory value that in the investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile
- Worsens (increases) to Grade 2 or higher based on the Sponsor's Grading for Laboratory Values

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 20, as shown in Table 7). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF. SAEs will be collected for 12 weeks after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the

investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the ADCOMS, ADAS-cog$_{14}$, MMSE, and CBB (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE.

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.11 for a description of the C-SSRS).

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

**Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.**

### Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

| | |
|---|---|
| Mild | Discomfort noticed, but no disruption of normal daily activity |
| Moderate | Discomfort sufficient to reduce or affect normal daily activity |
| Severe | Incapacitating, with inability to work or to perform normal daily activity |

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

## Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

*Classification of Causality*

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

#### 9.5.1.5.2 Serious Adverse Events and Other Events of Interest

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of

SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, other events of interest include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error; any treatment-emergent significant laboratory abnormality; any seizures, ocular herpes, herpes zoster, or severe infection; any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a "yes" answer to Type 4 or 5 suicidal ideation, or a "yes" response to any suicidal behavior on the C-SSRS. These events of interest are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with events of interest are to be reported on the eCRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

#### 9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 4. Subjects should be in a seated or supine position during blood collection. Table 6 and Table 7 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

See Section 9.3.3 for safety withdrawal criteria related to absolute counts of CD4, CD8, and B lymphocytes, and for lymphocyte subset counts.

## Table 4 Clinical Laboratory Tests

| Category | Parameters |
|---|---|
| **Hematology** | Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils) |
| **Chemistry** | |
| **Electrolytes** | Bicarbonate, calcium, chloride, phosphate, potassium, sodium |
| **Liver function tests** | Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin |
| **Renal function tests** | Blood urea/blood urea nitrogen, creatinine |
| **Other** | Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid |
| **Urinalysis** | Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells |
| **Other** | Lymphocyte subset analyses (see Table 5). Regulatory T cells will be measured using CD4, CD25, and CD127 cell surface markers and FoxP3 intracellular marker.<br>Ig analyses (IgG, IgA, and IgM).<br>Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]).<br>Serum pregnancy test (females of child bearing potential only)<br>Tuberculosis Interferon Gamma Release Assays<br>Tests for thyroid function and vitamin B12<br>Blood sample for storage for subsequent testing of immune status<br>Cerebrospinal fluid sampling |

**HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, Ig = immunoglobulin.**

The 8 different surface markers (CD3, CD4, CD8, CD45, CD19, CD16, CD56, and CD14) will be measured in order to provide the lymphocyte subset data as shown in Table 5. In addition, Regulatory T cells will be measured using CD4, CD25, and CD127 cell surface markers and FoxP3 intracellular marker.

## Table 5 Lymphocyte Subtyping

| Cell Type | Cell Surface Markers |
|---|---|
| T lymphocytes | CD3 |
| T helper cells | CD3+, CD4 |
| Cytotoxic T cells | CD3+, CD8 |
| Mature B cells | CD3-, CD19 |
| Natural killer cells | CD3-, CD16, CD56 |
| Macrophages | CD14 |

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the case report form [CRF] Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

For laboratory abnormalities meeting the criteria of SAEs (see Section 9.5.1.5.2), the site must fax or email the SAE report including the laboratory report (as regionally required) to the sponsor using the SAE form (see Section 9.5.4.1).

#### 9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [bpm], respiratory rate [per minute], body temperature [in centigrade], and weight [kg]) will be obtained at the visits designated in Table 6 and Table 7 by a validated method. Measurements of semi-supine BP and heart rate will be obtained. All BP measurements should be performed on the same arm, preferably by the same person.

#### 9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination will be performed at Screening as described in Section 9.5.1.2.1. At Baseline and during the Randomization Phase, routine physical examinations will take place as shown in Table 7. These examinations will include the cardiovascular system, respiratory system, and neurological system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

#### 9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 6 and Table 7. Twelve-lead standard ECGs will be recorded in triplicate (1 minute apart) after subjects have been resting in the supine position for at least 5 minutes.

On any study day when ECG, vital signs, and blood samples are taken, these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.5.2), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Section 9.5.4.1).

#### 9.5.1.5.7 SAFETY MRI

Safety brain MRI assessments will be performed at the times shown in Table 6 and Table 7. Additional safety MRI scans can be performed at unscheduled visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

Safety MRIs will be acquired using a standardized procedure that will include fluid-attenuated inversion recovery (FLAIR), gradient-echo, T1, and diffusion-weighted sequences to determine the presence of focal lesions including, but not limited to, evidence for ischemic and hemorrhagic stroke, subdural hematoma, neoplasm, arteriovenous malformation, micro and macrohemorrhages, superficial siderosis, lacunar infarcts, white matter abnormalities, and vasogenic edema. The imaging sequence for the Screening/safety MRI will include: T2 weighted anatomic MRI to rule out major white matter changes, cerebral infarction or other structural lesions, and a high-resolution 3D T1-weighted scan with isotropic voxels with volumes of 1 $mm^3$ or less. In addition, both FLAIR for the detection of vasogenic edema and T2* Gradient Recall Echo for the detection of microhemorrhages will be acquired. The 3D dataset will be reconstructed in transverse slices in Digital Imaging and Communications in Medicine format. The results of this MRI assessment will also be used as the Baseline Period MRI, against which changes after drug administration will be compared. Further details of the MRI protocol can be found in the Imaging Acquisition Guideline. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, and 18 and at the second Follow-Up Visit (Visit 20). In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

At any time during the treatment period, subjects will be discontinued from study drug if they develop any of the following features on MRI: vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage. All of these features must be reported as study specific AEs (or AEs of special interest). These subjects will undergo an ED Visit within 7 days after discontinuation and Follow-Up Visits at 4 weeks and 12 weeks after the last dose of treatment. Subjects will also undertake an Unscheduled Visit (with MRI) at approximately 30 days after the visit at which such MRI features were first

identified. Additional visits may be arranged if clinically indicated in the opinion of the investigator, and may occur later than 12 weeks after the final dose of study drug.

#### 9.5.1.5.8 DERMATOLOGICAL ASSESSMENT

Assessments by a dermatologist will be performed at the times shown in Table 6 and Table 7. These assessments will specifically include evaluation of any areas of depigmentation or any rash.

In addition, subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their caregiver or informants will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or infection, and the investigator will be required to review such AEs as soon as possible and consider an unscheduled physical and dermatological evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF. Physical examination may be undertaken where indicated. Treatment-emergent abnormal dermatological findings should be reported as AEs.

#### 9.5.1.5.9 NEUROLOGICAL EXAMINATION

Neurological examinations will be performed at Baseline and at regular intervals during the study by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations as shown in Table 6 and Table 7. Details of these examinations will be captured in an eCRF. The neurological examinations will monitor for new symptoms and signs which will then alert the investigator to consider new CNS pathology (especially slowly-evolving neurological conditions that may not lead to prominent symptoms). Examples of neurological signs that may indicate new CNS pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. In such a situation, the investigator should consider (but not limited to) demyelination in the differential diagnoses, and should discuss with the sponsor's medical monitor further investigations or treatment, which will be decided case by case. Neurological examinations will also include the assessment of cranial nerve function, especially the olfactory nerve. Treatment-emergent abnormal neurological findings should be reported as AEs.

#### 9.5.1.5.10 PREGNANCY TEST

At Screening, females of childbearing potential will have a serum pregnancy test. At Baseline and during the Treatment Phase, urine samples will be obtained from females of childbearing potential for pregnancy tests (see Table 7).

#### 9.5.1.5.11 COLUMBIA SUICIDE SEVERITY RATING SCALE

An assessment of suicidal ideation and behavior using the C-SSRS will be performed at the designed time points in Table 6 and Table 7. A "yes" answer to Type 4 or 5 suicidal ideation or a "yes" response to any suicidal behavior queries will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

#### 9.5.1.5.12 BIOMARKER SAMPLES

As noted in Section 9.5.1.2.3 and Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be tested in the event that a subject develops AEs that warrant further investigation.

### 9.5.2 Schedule of Procedures/Assessments

#### 9.5.2.1 Schedule of Procedures/Assessments

Table 6 presents the schedule of procedures/assessments for the Prerandomization Phase. Screening assessments will be organized into 4 tiers (see below and Figure 2).

Table 7 presents the schedule of procedures/assessments for the Randomization Phase.

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

| Phase | Prerandomization | |
|---|---|---|
| **Visit** | **Screening (Visit 1)** | **Baseline (Visit 2)** |
| **Procedures/ Assessments (to be completed in a maximum of 50 days)** | | |
| Informed consent (subject and caregiver or informant) | X (Tier 1) | |
| Demographics | X (Tier 1) | |
| Medical history[a] | X (Tier 1) | |
| Prior / concomitant medications[b] | X (Tier 1) | X |
| Vital signs including weight[c] | X (Tier 1) | X |
| Height | X (Tier 1) | |
| Complete physical examination | X (Tier 1) | |
| Routine physical examination | | X |
| CBB and ISLT[d] | X (Tier 1) | X |
| MMSE[d] | X (Tier 1) | X |
| CDR[d] | X (Tier 1) | X |
| FAQ[d] | X (Tier 1) | X |
| ADAS-cog14[d] | | X |
| 15-item Geriatric Depression Scale | X (Tier 2) | |
| Modified Hachinski ischemic scale | X (Tier 2) | |
| C-SSRS | X (Tier 2) | X |
| 12-lead ECG[e] | X (Tier 2) | X |
| Blood and urine for clinical laboratory tests[f] | X (Tier 2) | X |
| Blood for lymphocyte subset analyses[g] | X (Tier 2) | X |
| Blood for Ig analyses[h] | X (Tier 2) | X |
| Blood for viral screen[i] | X (Tier 2) | |
| Blood for thyroid function tests[j] | X (Tier 2) | |
| Test for previous TB exposure | X (Tier 2) | |
| Urine drug screen | X (Tier 2) | |
| Serum pregnancy test (females of childbearing potential only) | X (Tier 2) | |
| Urine pregnancy test (females of childbearing potential only) | | X |
| Safety and Volumetric MRI[k] | X (Tier 3) | |
| Amyloid PET scan[l] | X (Tier 4) | |
| Inclusion and Exclusion criteria | X (All tiers) | X |
| Adverse events | X (All tiers) | X |
| CSF sampling for PK, PD and storage[m] | | X |
| Blood for PK assessments[n] | | X |
| Blood for PD assessments[o] | | X |
| Blood sample for pharmacogenomics | | X |
| Blood sample for storage for immune status[p] | | X |
| Dermatological assessment[q] | | X |
| Neurological examination[r] | | X |
| Ophthalmic assessment | | X |

AchEI = acetylcholinesterase inhibitor, AD = Alzheimer's disease, ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV = herpes simplex virus, Ig = immunoglobulin, ISLT = International Shopping List Task (immediate and delayed recall), LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PD = pharmacodynamics, PK = pharmacokinetics, PET = positron emission tomography, TB = tuberculosis.

Screening assessments/procedures have been organized into 4 distinct tiers. All assessments and procedures in each tier should be completed (see Figure 2), and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Similarly, all screening assessments and procedures must be completed, and eligibility to continue in the study confirmed, before any baseline assessments and procedures commence. Adverse events and eligibility against inclusion and exclusion criteria must be assessed at each stage within the Screening Visit and at the Baseline Visit.

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

All screening and baseline assessments are to be completed within 50 days. The interval between availability of the results of the last screening assessment (PET scan) and the first baseline (Visit 2) assessments should be as short as possible and ideally should not exceed 7 days. Visit 3 (Randomization) (see Table 7) should occur 7 to 10 days after completion of the Baseline visit (Visit 2) and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion #19 into account. Thus, the total Prerandomization Phase may be up to 60 days.

a: To include: mild cognitive impairment and AD history; history of TB, vaccination history against and infections due to varicella zoster virus (chickenpox and herpes zoster or shingles); infections due to HSV1 (orolabial herpes or cold sores) and 2 (genital herpes). Medical history of infections to include: onset, duration, relapse frequency, severity, and treatments.

b: Prior and concomitant medications include AChEIs and memantine, and other medications for cognitive decline.

c: Weight, respiratory rate, body temperature, semi-supine blood pressure, and heart rate will be obtained.

d: To be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments/procedures (eg, physical examination, ECG, blood draws). The order of assessments is: MMSE, CDR, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall) at Screening; and MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall) at the Baseline Visit. At visits where the CDR or FAQ are conducted, the investigator will determine whether the caregiver or informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

e: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

f: Clinical laboratory tests include hematology, clinical chemistry and urinalysis, and include measurement of vitamin B12.

g: Lymphocyte subsets to be measured include CD4 (T helper cells), CD8 (cytotoxic T cells), CD19 (B cells), CD16/CD56 (natural killer cells) and CD14 (macrophages). Regulatory T cells will also be measured (CD4, CD25, and CD127, FoxP3). Viability staining may also be employed.

h: Igs to be analyzed include IgG, IgA and IgM.

i: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

j: Thyroid function tests include thyroid stimulating hormone, free triidothyronine and free thyroxine.

k: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images in addition to sequences for resting state functional MRI. MRI will be read by an approved central reader. Volumetric MRI for PD assessment will be performed in all subjects immediately following the safety MRI assessments in the same imaging session.

l: PET scanning will be performed with a locally approved β-amyloid imaging agent, eg, Amyvid if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. The PET image will be centrally read for the purpose of determining eligibility for inclusion into the study.

m: CSF will be collected by LP after fasting (preferred), or at least 2 hours after the most recent meal. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The timing of the Baseline LP needs to be scheduled carefully such that subsequent LPs (Visit 7 and Visit 18) can be performed at a similar time of day (±1 hour) for each individual subject. The LP must be performed after the cognitive tests have been performed; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. The CSF sample will be used for PK and PD assessments. A CSF sample will also be stored for testing in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection).

n: The PK blood sample should be collected shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal.

o: The PD blood sample should be collected shortly after completing the LP. The sample should be collected at fasting or at least 2 hours after the most recent meal.

p: A blood sample will be collected at Baseline and stored. In the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

q: Assessments will be by a dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. See Section 9.5.1.5.8 for further details.

## Table 6 Schedule of Procedures/Assessments in Study 202: Prerandomization Phase (Visit 1 and Visit 2)

r: To be performed by either a neurologist or a physician with comparable training and experience in undertaking neurological examinations. Section 9.5.1.5.9 details what is included in the neurological examination.

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| **Phase** | **Randomization** | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | | | | | **Follow-Up** | | |
| **Visit[a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16[b]** | **17** | **18[b]** | **ED[d]** | **19[c]** | **20[c]** | **UNS Visit[e]** |
| **Day** | **1** | **8** | **15** | **22** | **29** | **43** | **57** | **71** | **85** | **113** | **141** | **183** | **274** | **365** | **456** | **547** | | **575** | **631** | |
| **Week** | **1** | **2** | **3** | **4** | **5** | **7** | **9** | **11** | **13** | **17** | **21** | **27** | **40** | **53** | **66** | **79** | | **83** | **91** | |
| **Weeks elapsed since first dose** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **10** | **12** | **16** | **20** | **26** | **39** | **52** | **65** | **78** | | **82** | **90** | |
| **Nominal months elapsed since first dose** | **0** | | | | **1** | | **2** | | **3** | **4** | **5** | **6** | **9** | **12** | **15** | **18** | | **19** | **21** | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | |
| Routine physical examination | X | | | | X | | X | | X | | | X | X | X | X | X | X | X | X[y] | X |
| Inclusion and Exclusion criteria | X | | | | | | | | | | | | | | | | | | | |
| Vital signs[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[y] | X |
| Respiratory rate | | | | | X | | X | | X | X | X | X | X | X | X | X | X | X | X[y] | X |
| Weight | | | | | | | | | X | | | X | X | X | X | X | X | | X | X |
| Dermatological assessment[g] | | | | | | | | | X | | | X | X | X | X | X | X | | X | X |
| Neurological examination[h] | | | | | | | | | | | | X | | X | | X | X | X | X | X |
| Opthalmic examination[i] | | | | | | | | | | | | | | | | | | | | X |
| Concomitant medications[j] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG[k] | | | X | | X | | X | | X | | | X | | X | | X | X | X | X[y] | X |
| Clinical biochemistry and urinalysis | | | X | | X | | X | | X | | | X | X | X | X | X | X | X | X[y] | X |
| Complete blood count | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[y] | X |
| Blood for lymphocyte subset analyses[l] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[y] | X |
| Blood for Igs[m] | | | | | X | | X | | X | | | X | | X | | X | X | X | X[y] | X |
| Urine pregnancy test (females of CBP only) | X[n] | | | | | | | | X | | | X | X | X | X | X | X | X | | X |
| Blood sample for storage for immune status[o] | | | | | X | | | | X | | | X | | X | | X | X | | | X |

## Table 7 Schedule of Procedures/Assessments in Study 202: Randomization Phase (Visit 3 through Visit 20)

| **Phase** | **Randomization** | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Treatment** | | | | | | | | | | | | | | | | | **Follow-Up** | | |
| **Visit[a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16[b]** | **17** | **18[b]** | **ED[d]** | **19[c]** | **20[c]** | **UNS Visit[e]** |
| **Day** | **1** | **8** | **15** | **22** | **29** | **43** | **57** | **71** | **85** | **113** | **141** | **183** | **274** | **365** | **456** | **547** | | **575** | **631** | |
| **Week** | **1** | **2** | **3** | **4** | **5** | **7** | **9** | **11** | **13** | **17** | **21** | **27** | **40** | **53** | **66** | **79** | | **83** | **91** | |
| **Weeks elapsed since first dose** | **0** | **1** | **2** | **3** | **4** | **6** | **8** | **10** | **12** | **16** | **20** | **26** | **39** | **52** | **65** | **78** | | **82** | **90** | |
| **Nominal months elapsed since first dose** | **0** | | | | **1** | | **2** | | **3** | **4** | **5** | **6** | **9** | **12** | **15** | **18** | | **19** | **21** | |
| **Procedures/ Assessments** | | | | | | | | | | | | | | | | | | | | |
| CBB and ISLT[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| MMSE[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| CDR[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| ADAS-$cog_{14}$[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| FAQ[p] | | | | | | | | | X | | | X | X | X | X | X | X | X | X | |
| C-SSRS | | | | | X | | X | | X | | | X | X | X | X | X | X | X | X[y] | X |
| Safety and Volumetric MRI[q] | | | | | | | | | | | | X | | X | | X | X | | X | X |
| Amyloid PET[r] | | | | | | | | | | | | | | | | X | X | | | |
| Telephone contact[s] | | | X | | X | | | | X | | | X | | X | | X | X | | | X |
| Blood for PK[t] | | | X | | X | | | | X | | | X | | X | | X | X | | | X |
| Blood for PD[u] | | | X | | X | | | | X | | | X | | X | | X | X | X | X | |
| CSF sampling for PK and PD[v] | | | | | X | | | | | | | | | | | X | X | | | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Sleep/dream questionnaire[w] | | | | | | | | | | | | | | | | | | | | X |
| Randomization | X | | | | | | | | | | | | | | | | | | | |
| Dispense study drug[x] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |

## Notes for Table 7

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBB = CogState Brief Battery, CBP = childbearing potential, CDR = Clinical Dementia Rating scale, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), Ig = immunoglobulin, ISLT = International Shopping List Task, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, UNS = unscheduled.

a: Visit 3 should be conducted 7 to 10 days after completion of the Baseline visit (Visit 2) assessments and confirmation of eligibility to continue in the study, unless additional time is required to take Exclusion Criterion #19 into account. A window of ±3 days will be permitted for Visit 4 to 14 inclusive. A window of ±10 days will be permitted for Visit 15 to 18 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since first dose" at subsequent visits.

b: For subjects who discontinue taking study drug prematurely, the only assessments required at Week 53 (Visit 16) and Week 79 (Visit 18) are the MMSE, CDR, ADAS-cog$_{14}$, CBB, and ISLT.

c: All subjects, regardless of whether they complete all 18 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 19 and Visit 20 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up period.

d: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 19 and Visit 20, respectively). Subjects will also be scheduled to return to the study site to undertake limited efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, CBB, and ISLT) at Week 53 (Visit 16) and Week 79 (Visit 18) if they withdrew from study drug before these time points.

e: Unscheduled visits may be conducted at any time that safety or safety MRI data indicate per protocol or as clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

f: Measurements of body temperature and semi-supine blood pressure and heart rate will be obtained.

g: Assessments will be by a dermatologist. These assessments will specifically include evaluation of any areas of depigmentation or any rash. Additional UNS dermatological assessments should be conducted in response to any dermatological AEs of concern, eg, depigmentation, rash, herpetic lesion.

h: Examples of neurological signs that may indicate new central nervous system pathology that may need further investigation include (but not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

i: If the subject experiences visual disturbances during the course of the study, the subject will be referred to a specialist for a further ophthalmic examination including a retinal examination.

j: Please refer to Section 9.4.7, which details prohibited and permitted medications in the study and associated timeframes.

k: 12-lead standard ECGs will be recorded in triplicate (1 minute apart).

l: Lymphocyte subsets to be measured include CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [NK cells] and CD14 [macrophages]). Regulatory T cells will also be measured (CD4, CD25 and CD127, FoxP3). Viability staining may also be employed.

m: Igs to be analyzed include IgG, IgA, and IgM.

n: An additional assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

o: Blood samples will be collected and stored. In the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

p: These assessments are to be completed in the morning whenever possible, or consistently at the same time of day. These assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The order of assessments will be: MMSE, CDR, ADAS-cog14, FAQ, ISLT (immediate recall), CBB, and ISLT (delayed recall). At visits where the CDR or FAQ are conducted, the investigator will determine whether the informant must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

q: Safety MRIs will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images in addition to sequences for resting state functional MRI. MRI will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 14, 16, and 18 and 20. In the event of an Unscheduled Visit, the investigator in consultation with the sponsor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A volumetric MRI sequence will be collected in all subjects immediately following all safety MRI assessments.

r: PET scanning will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks.

s: Site staff will contact the subject or the caregiver or informant the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the caregiver or informant, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

t: Two PK samples will be obtained: one at predose (trough) and another 1 to 6 hours postdose at Visit 5, Visit 11, Visit 14 and Visit 16 and 4 to 8 hours postdose at Visit 7 and Visit 18 (or ED). Therefore, subjects or their caregivers or informants must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 7 and Visit 18 (or ED) the PK blood sample should be collected shortly after completing the LP.

u: PD blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day. At Visit 7 and Visit 18 (or ED) the PD blood sample should be collected shortly after completing the LP.

v: All visits at which CSF samples are scheduled to be taken also include blood PK and PD assessments and so the subject will be dosed at the clinic on these days. CSF will be collected by LP 4 and 8 hours postdose and at the same time of day as the subject's Baseline LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. The LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample.

w: Subjects reporting adverse events relating to abnormal dreams or sleep-related events, or sleep terror will be questioned on the frequency and impact of these events.

x: The first dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time for post-dose medical observation.

y: Only if clinically significant abnormalities are found at Visit 19 and the investigator considers it necessary to repeat at Visit 20. However, lymphocyte subsets and Igs should be repeated at Visit 20 if they were outside of the normal range (regardless of clinical significance) at Visit 19.

#### 9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 6 and Table 7 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 4 tiers (see Table 6, Section 9.1.1.1, and Figure 2). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 8 presents the number of blood and CSF samples, and the total volume of blood and CSF that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety.

**Table 8 Summary of Blood and CSF Sample Volumes**

| Assessment | Total number of collection time points | Sample volume, number of time points x volume per collection (mL) | | Total volume (mL) |
|---|---|---|---|---|
| | | Screening and Baseline Periods | Treatment and Follow-Up Periods | |
| **Blood** | | | | |
| Chemistry | 12 | 2 x 2 mL | 10 x 2 mL | 24 mL |
| Hematology | 18 | 2 x 5 mL | 16 x 5 mL | 90 mL |
| Lymphocyte subset analyses | 18 | 2 x 4 mL | 16 x 4 mL | 72 mL |
| IgA, IgM, IgG | 9 | 2 x 2 mL | 7 x 2 mL | 18 mL |
| Thyroid function tests (thyroid stimulating hormone, free triidothyronine and free thyroxine) | 1 | 1 x 3 mL | None | 3 mL |
| Viral screen (Hepatitis A and B) | 1 | 1 x 4 mL | None | 4 mL |
| Vitamin B12 | 1 | 1 x 2 mL | None | 2 mL |
| Serum pregnancy test | 1 | 1 x 2 mL | None | 2 mL |
| Tuberculosis (interferon-gamma release assays) | 1 | 1 x 3 mL | None | 3 mL |
| Blood for immune status | 6 | 1 x 2 mL | 5 x 2 mL | 12 mL |
| PD sample | 9 | 1 x 4 mL | 8 x 4 mL | 36 mL |
| PK analysis | 7 | 1 x 2 mL | 6 x 2 mL | 14 mL |
| Pharmacogenetic sample | 1 | 1 x 6 mL | None | 6 mL |
| All blood samples, total volume collected | | 54 mL | 232 mL | 286 mL |
| **CSF sampling** | | | | |
| PD and PK samples | 3 | 1 x 10 mL | 2 x 10 mL | 30 mL |

CSF = cerebrospinal fluid, Ig = immunoglobulin, PD = pharmacodynamics, PK = pharmacokinetic.

### 9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include vital signs, clinical laboratory assessments, physical examinations, ECG measurements, and reports of AEs. MRI will be used to detect vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a symptomatic microhemorrhage and is a standard evaluation to ensure subject safety. The C-SSRS has been endorsed by the FDA as a measure of potential suicidality (Guidance for Industry Suicidality).

A number of safety aspects have been built into the design of this study in light of the preclinical and clinical safety data with E2609, in addition to mitigating clinical risk in the progression from 14 days of dosing in the MAD study to 18 months of treatment in this Phase 2 study. Details are provided in Section 9.2.6.

### 9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Other Events of Interest

#### 9.5.4.1 Reporting of Serious Adverse Events

**All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.**

**Deaths and life-threatening events should be reported immediately by telephone. The immediate report should be followed up within 1 business day by emailing or faxing the completed SAE form.**

SAEs, regardless of causality assessment, must be collected up to 3 months after the last dose of study or through the last visit, whichever is longer. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

**For urgent safety issues**, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

#### 9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 30 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 30 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must discontinue study treatment.

#### 9.5.4.3 Reporting of Other Events of Interest

##### 9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

| | |
|---|---|
| Overdose | Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose |
| Misuse | Intentional and inappropriate use of study drug not in accordance with the protocol |
| Abuse | Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects |
| Medication error | Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject |

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

##### 9.5.4.3.2 Reporting of Significant Laboratory Abnormality

Any significant treatment-emergent laboratory abnormality observed during the clinical study should be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the laboratory abnormality does not meet serious criteria. If the significant laboratory abnormality does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

A laboratory result should be considered a treatment-emergent significant abnormality if the result:

- Is within normal limits at baseline and has increased in severity to meet the sponsor's grading criteria for laboratory values of Grade 3 or above
- Is outside normal limits at baseline and increases in severity to the sponsor's grading criteria for laboratory values of Grade 4 or above
- Is otherwise considered by the investigator to meet serious criteria as defined in Section 9.5.1.5.2

Significant laboratory abnormalities should not be listed as separate AEs or SAEs if they are considered to be part of the clinical syndrome that is being reported as an AE or SAE.

#### 9.5.4.3.3 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2) should be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet serious criteria. If the event does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

### 9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

### 9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

#### 9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

### 9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 19 and Visit 20, respectively) (see Section 9.1.2.3). See Table 7 for full details of the assessments to be performed at these visits. Subjects who discontinue study drug prematurely will also be scheduled to return to the study site to undertake limited efficacy assessments (MMSE, CDR, ADAS-cog$_{14}$, CBB, and ISLT) at Week 53 (Visit 16) and Week 79 (Visit 18), if these 2 visits have not already been performed.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who withdraw prematurely from the study will be withdrawn for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition eCRF.

A subject removed from the study for any reason may not be replaced.

### 9.5.6 Abuse or Diversion of Study Drug

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Potential Abuse-related Medication Handling Event eCRF.

### 9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

## 9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

### 9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

### 9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy assessments performed in this study.

## 9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, except for the Bayesian methods on the primary endpoint.

### 9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the statistical analysis plan, which will be finalized before the first interim efficacy analysis.

#### 9.7.1.1 Study Endpoints

See Section 9.2.3 for a discussion of the rationale for the selection and clinical relevance of the primary study endpoint. Further information on the derived ADCOMS is described in Section 9.5.1.3.1 and information on the individual assessments that are included within the ADCOMS is described in Section 9.5.1.2.2.

##### 9.7.1.1.1 PRIMARY ENDPOINT

- Change from baseline in the derived ADCOMS at 18 months of treatment in MCI/Prodromal subjects

##### 9.7.1.1.2 SECONDARY ENDPOINTS

Change from baseline in:

- Total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- CSF Aβ(1-x) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects
- The derived ADCOMS at 18 months of treatment in mild AD subjects

##### 9.7.1.1.3 EXPLORATORY ENDPOINTS

Change from baseline in:

- The derived ADCOMS at 12 months of treatment in MCI/Prodromal and mild AD subjects
- Total hippocampal volume at 12 and 18 months of treatment in mild AD subjects as measured by vMRI
- CSF Aβ(1-42) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects

- CSF Aβ(1-x) and Aβ(1-42) after 4 weeks and 18 months of treatment in mild AD subjects
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ in MCI/Prodromal and mild AD subjects
- CSF biomarkers of neurodegeneration (eg, tau and p-tau) at 18 months of treatment in MCI/Prodromal and mild AD subjects
- Plasma and CSF amyloid, and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild AD subjects
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and, 18 months in MCI/Prodromal and mild AD subjects as measured by vMRI
- Brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild AD subjects
- The population PK parameters of E2609 including the effect of intrinsic and extrinsic factors (including *NAT2* phenotype) in MCI/Prodromal and mild AD subjects

#### 9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol (PP) Analysis Set is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 serum concentration accompanied by a documented dosing history.
- The PD Analysis Set is the group of subjects who have a baseline PD measurement and at least 1 posttreatment PD measurement.

#### 9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for

screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: The number (percent) of randomized and treated subjects who completed the study and who withdrew from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and withdrew from the study. The primary reasons for discontinuation from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

Completion of Study Treatment: The number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for discontinuation from the study drug are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, inadequate therapeutic response, and other. The secondary reasons for discontinuation from the study are: AE, subject choice, and other.

#### 9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, MMSE and FAQ; categorical variables include sex, age group (≤65 years, age >65 years), race, ethnicity, *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI/Prodromal AD or mild AD).

#### 9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up period will also be recorded.

#### 9.7.1.6 Efficacy Analyses

***MCI/Prodromal Cohort***

The study in the MCI/Prodromal cohort is based on Bayesian adaptive design. Frequent interim analyses will be performed to assess the probability of early success and futility and to make early stopping decisions. Response adaptive randomization will be used to update the randomization probability among treatment groups at each interim analysis. Key definitions relevant to the Bayesian aspects of the adaptive design are given below.

**Study Definitions**

- **Maximum Effective Dose ($d_{Max}$):** The dose that achieves the greatest treatment effect.
- **$ED_{90}$:** The lowest dose that achieves at least 90% of the $d_{Max}$ treatment effect in the derived ADCOMS.
- **Early Success:** The study in the MCI/Prodromal cohort will meet early success criteria if the probability that the $ED_{90}$ at 18 months of treatment achieves 25% improvement over placebo is at least 80%. Early success is achieved before all MCI/Prodromal subjects complete 18 months of treatment and can only be determined after at least 200 MCI/Prodromal subjects have been randomized. If early success is declared before full randomization, the randomization of new MCI/Prodromal subjects will stop but subjects already randomized into the study will receive the full 18 months of treatment (following confirmation from the Sponsor's Senior Management).
- **Futility:** The study in the MCI/Prodromal cohort will meet statistical futility criteria if the probability that the $ED_{90}$ is better than placebo by the clinically significant difference of 25% is less than 5% at 18 months of treatment. The statistical futility boundary is binding; if the statistical futility boundary is crossed the study will be considered to have failed.
- **Study Success:** The study in the MCI/Prodromal cohort will be considered a success if an $ED_{90}$ at 18 months treatment has at least an 80% probability of achieving 25% improvement over placebo at either an interim analysis or at the final analysis.

***The Mild AD Cohort***

The analysis of the Mild AD cohort is based on the group sequential design. Interim analyses in the Mild AD cohort will only be performed after the MCI/Prodromal cohort crosses the early success boundary. The early efficacy signal based on the change from baseline of ADCOMS at 18 months is defined as crossing the interim-analysis boundaries for overwhelming efficacy in the mild AD population. The O'Brien-Fleming (OF) boundaries based on Lan-DeMets alpha spending function will be used to assess overwhelming efficacy. The corresponding OF boundaries based on *P* values will be 0.076, 0.0221, and 0.0423 for the first, second, and final analyses, respectively, according to 2 planned interim analyses at the 60% and 80% information fraction.

#### 9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on MCI/Prodromal subjects from the FAS with the prespecified censoring rule applied. The primary endpoint is the change from baseline to 18 months in the derived ADCOMS. The dose-response of the primary endpoint is modelled with a first-order normal dynamic linear model, where Normal and Inverse-Gamma priors are used. The primary efficacy analysis will calculate the Bayesian posterior probability that the dose identified is the most likely $ED_{90}$ dose that achieves 25% improvement over the placebo arm. At each interim analysis and the final analysis, 2 Bayesian probabilities will be summarized for each active dose: the probability it is the $ED_{90}$ dose and the probability of achieving 25% improvement over the placebo arm.

For the clinical efficacy data (ie, derived ADCOMS, MMSE, CDR, ADAS-cog, CBB, ISLT, and FAQ) subjects will be censored at the time of initiation of treatment with AChEIs or memantine, if they were not on these medications at the time of Baseline cognitive assessment (Visit 2), and will be censored at the time of dose adjustment of AChEIs or memantine if they were already on stable treatment with these medications at the time of Baseline cognitive assessment (Visit 2). The value of the primary endpoint for censored subjects will be imputed using data up to the censoring time and Bayesian longitudinal modeling.

After unblinding, the primary endpoint will be analyzed using the Bayesian methods described above as well as conventional statistical methods. The following additional Bayesian analyses will be conducted as sensitivity analyses:

- The primary endpoint will be analyzed regardless of initiation of treatment, or dose adjustment, with AChEIs or memantine using the same Bayesian analysis method as primary analysis. This is an intent-to-treat analysis without any censoring.
- In case of early success, the primary analysis as well as the above sensitivity analyses will be repeated after all subjects have completed 18 months of treatment or have been lost to follow-up.

Statistical methods for the final conventional analyses will use a mixed-effects model with repeated measures (MMRM) on the change from baseline in the derived ADCOMS at 18 months. The model will include treatment groups, randomization stratification variables (the presence or absence of ongoing treatment with AChEIs or memantine or both, and *ApoE4* status), and baseline ADCOMS as covariates. These analyses will be performed on the FAS as well as the PP set. In case of early success, the conventional analyses will also be performed using the data collected before the interim analysis.

#### 9.7.1.6.2 SECONDARY EFFICACY ANALYSES

***The MCI/Prodromal Cohort***

An MMRM will be used to analyze the following secondary endpoints:

- Change from baseline in total hippocampal atrophy at 12 and 18 months of treatment in MCI/Prodromal subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-x) after 4 weeks and 18 months of treatment in MCI/Prodromal subjects. Data from early discontinuations will also be included.

Comparisons between each treatment group and placebo will be performed.

***The Mild AD Cohort***

The MMRM will be used to analyze the change from baseline of derived ADCOMS at 18 months in mild AD. If there is no treatment group-by-population interaction in the overall study, the MMRM analysis will include all subjects (MCI/Prodromal or mild AD) in the overall study. Otherwise, the MMRM analysis will only include subjects in the mild AD cohort. The comparison between placebo and active doses will be performed within mild AD subjects regardless of subjects included in the MMRM analysis. Dunnett's method will be used to control for multiplicity due to multiple comparisons.

#### 9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

An MMRM will be used to analyze the following exploratory endpoints:

- Change from baseline in the derived ADCOMS at 12 months in MCI/Prodromal and mild AD subjects
- Change from baseline in total hippocampal atrophy at 12 and 18 months in mild AD subjects as measured by vMRI
- Change from baseline in CSF Aβ(1-42) after 4 weeks and 18 months in MCI/Prodromal subjects. Data from early discontinuations will also be included.
- Change from baseline in CSF Aβ(1-x) and CSF Aβ(1-42) after 4 weeks and 18 months in mild AD subjects. Data from early discontinuations will also be included.
- Change from baseline in the clinical assessments: ADAS-cog, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months in MCI/Prodromal and mild AD subjects
- Change from baseline in plasma and CSF amyloid and CSF BACE1 measurements after 4 weeks and 18 months of treatment, and during posttreatment follow-up in MCI/Prodromal and mild AD subjects
- Change from baseline in left and right hippocampal, whole brain, and total ventricular volume at 6, 12 and 18 months as measured by vMRI in MCI/Prodromal and mild AD subjects

A linear mixed-model will be used to analyze the following exploratory endpoints:

- Change from baseline in brain amyloid levels as measured by amyloid PET at 18 months in MCI/Prodromal and mild AD subjects
- Change from baseline in CSF biomarkers of neurodegeneration (eg, tau, p-tau) at 18 months of treatment in MCI/Prodromal and mild AD subjects

Data from early discontinuations will also be used as appropriate. Comparisons between each treatment group and placebo will be performed.

A linear mixed-model with repeated measures will be used to determine the relationship between the following endpoints:

- Change from baseline in the derived ADCOMS score and the change from baseline in biomarkers in CSF at 18 months in MCI/Prodromal and mild AD subjects
- Change from baseline in the derived ADCOMS score and change from baseline in imaging biomarkers (hippocampal, whole brain, and total ventricular volumes) at 12 and 18 months in MCI/Prodromal and mild AD subjects

*ApoE* status for heterozygous and homozygous E4 carriers will be included in the model to assess the effect of *ApoE* status in this relationship.

#### 9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

##### 9.7.1.7.1 PHARMACOKINETIC ANALYSES

The Safety Analysis Set will be used for individual E2609 concentration listings. The PK Analysis Set will be used for summaries of E2609 concentrations.

##### 9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Pharmacodynamic, PGx, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate statistical analysis plan. Please also refer to Appendix 3.

**Pharmacodynamic Analyses**

The PD Analysis Set will be used for the summaries and analyses of PD biomarkers (CSF and plasma biomarkers, MRI endpoints). CSF Aβ(1-x), Aβ(1-42), t-tau, p-tau, and BACE1 will be assessed and data will be presented graphically. Baseline levels and changes in t-tau and p-tau will be correlated with changes in CSF Aβ(1-42), imaging markers, and *ApoE4* status.

Summary statistics for CSF biomarkers will be assessed for evidence of a dose relationship.

**Pharmacokinetic and Pharmacodynamic Analyses**

The PK/PD relationship between CSF biomarker levels and exposure to E2609 in CSF will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. The PK/PD relationship between plasma PK parameters with other biomarkers may also be explored using similar methods.

Additionally, the relationship between plasma and CSF exposure to E2609 and the derived ADCOMS at 18 months, and the relationship between plasma and CSF exposure to E2609 and the change from baseline for 18 months in the ADAS-cog, the CDR, and the MMSE, will be explored graphically. Any emergent relationship will be explored through population PK/PD modeling.

Exposure-safety analyses may also be conducted.

**Pharmacogenomic Analyses**

Blood samples will be used to determine the *ApoE* genotype and the *NAT 2* phenotype of subjects enrolled in this study. The genomic DNA samples may also be stored and used as described in Section 9.7.1.7.2. Details of PGx testing may be provided and reported separately.

#### 9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, and vital sign measurements will be summarized by treatment group using descriptive statistics.

##### 9.7.1.8.1 Extent of Exposure

The extent of exposure to study drug will be summarized as cumulative extent of exposure in 3-month intervals. The number and percent of subjects will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics in 3-month intervals. The number and percent of subjects will be presented by treatment group.

##### 9.7.1.8.2 Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 17.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

Adverse events will be summarized by the following subgroups: *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI/Prodromal or mild AD).

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

#### 9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

Lymphocyte subsets (ie, CD4 [T helper cells], CD8 [cytotoxic T cells], CD19 [B cells], CD16/CD56 [natural killer cells] and CD14 [macrophages]) and regulatory T cells will be summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets will also be displayed graphically over time by dose.

Serum IgG, IgM, and IgA will be measured and summarized in the same manner as other laboratory parameters.

#### 9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

#### 9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to the end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 ms
- QTc interval >480 ms
- QTc interval >500 ms

Change from baseline in QTc interval:

- QTc interval increases from baseline >30 ms
- QTc interval increases from baseline >60 ms

#### 9.7.1.8.6 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog$_{14}$, MMSE, CDR, and CBB (see Section 9.7.1.6).

### 9.7.2 Determination of Sample Size

#### 9.7.2.1 Sample Size Rationale in the MCI/Prodromal Cohort

Primary endpoint – derived ADCOMS

The sample size and design characteristics to test the hypothesis for the primary objective based on the primary endpoint, change from baseline of the derived ADCOMS at 18 months, were determined by means of simulations. Extensive study simulations have shown that a total of 500 subjects will be sufficient to demonstrate that the most likely ED$_{90}$ dose achieves a 25% improvement over placebo with a probability of at least 80% in the interim and final analyses. There is at least a 90% probability of study success for the dose response scenarios where treatment was considered to have a clinically meaningful treatment effect. Simulations have also shown that if there is no obvious dose effect, the probability of falsely claiming superiority to placebo is at most 5%.

For each of the 4 treatment groups (3 active doses and placebo) the final number of subjects per group will differ depending on the observed interim treatment responses. The simulation plan will be an appendix to the statistical analysis plan and will present further details.

vMRI

The null hypothesis is that there is no difference between active dose and placebo. There are 3 null hypotheses corresponding to 3 active doses. The alternative hypothesis is that at least 1 null hypothesis is false (1-sided). The null hypotheses will be tested using Dunnett's method with 1-sided alpha of 0.05. The statistical power was estimated through simulation for a moderate dose-response assumption that the percent reduction in change from baseline of total hippocampal volume compared with placebo would be 15%, 20%, and 25% corresponding to the 3 doses, respectively. The estimated power for the actual planned study sample size is 78% at 18 months assuming an attrition rate of 20% at 18 months. Under a stronger dose-response assumption (ie, the percent reduction in change from baseline of total hippocampal volume compared with placebo is twice as much as that in the moderate dose-response assumption), the estimated power is at least 99% at 18 months.

Amyloid PET

The null and alternative hypotheses and the statistical test are the same as those for vMRI. To estimate the sample size for the amyloid PET imaging subgroup at 18 months, a common SD of the change from baseline was estimated at 0.33 and a reasonable mean difference between treatment and placebo was estimated as 0.25 (standardized uptake value ratio [SUVR]). Assuming a moderate dose-response, the best dose would achieve a difference of 0.25 (SUVR) and the middle and low doses would achieve a difference of 0.2 and 0.15 (SUVR), respectively, this would require a total of 100 subjects from all 4 arms at 18 months to achieve 80% power.

#### 9.7.2.2 Sample Size Rationale for the Mild AD Cohort

ADCOMS at Month 18

The null hypothesis is that there is no difference between active dose and placebo. There are 2 null hypotheses corresponding to 2 active doses. The alternative hypothesis is that at least 1 null hypothesis is false. The null hypotheses will be tested using Dunnett's test with 2-sided alpha of 0.05 as described for the mild AD cohort in Section 9.7.1.6.2. The statistical power was estimated through simulation for the dose-response assumption that the percent reduction in change from baseline of ADCOMS at 18 months compared with placebo would be 33% and 50% corresponding to the 2 doses, respectively. The estimated power for the actual planned 200 mild AD subjects is at least 80% assuming a 2-sided alpha of 0.05.

### 9.7.3 Interim Analysis

***The MCI/Prodromal Cohort***

The Bayesian interim analyses and response adaptive randomization will be conducted by an unblinded external independent analysis group in accordance with the protocol. Oversight of the Bayesian interim analyses and response adaptive randomization will be conducted by an independent unblinded committee that has expertise with Bayesian adaptive design in clinical studies to ensure that the response adaptive randomization process and interim analyses perform as expected. The analysis group will provide the interim analysis outcomes to the committee at each interim analysis. The committee will ensure the integrity of the interim analysis and response adaptive randomization process through review of efficacy data. In addition, the committee will act in an independent advisory capacity to monitor the Bayesian interim analysis outcomes according to the early success and futility boundaries prespecified in the protocol. The committee will not be charged with any subject safety issues; this will remain the responsibility of the DSMB.

If the predefined early success criteria are met during the recruitment period, further recruitment and enrollment of MCI/Prodromal subjects into the study will stop (following confirmation from the Sponsor's Senior Management) and all currently randomized subjects will complete the full 18 months of treatment. No further interim analyses will be conducted after achieving early success.

If the predefined threshold for futility is reached, no additional subjects will be randomized into the study and the treatment of subjects already randomized into the study will stop and the study will be declared as "failed". All subjects will be monitored for safety for 3 months following their last dose.

If neither early success nor futility is reached and the study reaches full randomization, all subjects will complete 18 months of treatment. Interim efficacy analyses will be conducted every 3 months after full randomization is reached to assess futility and early success until all subjects complete 18 months of treatment. After full randomization, all study subjects will stop treatment only in the event of futility.

The DSMB will continue to monitor the safety aspects of the study throughout Stage A and Stage B. Details will be provided in the DSMB Charter. The study may be stopped for safety at any time.

An interim analysis will be conducted for safety when the first 60 MCI/Prodromal subjects have completed 12 weeks of treatment.

The first Bayesian adaptive interim analysis will be conducted when 100 MCI/Prodromal subjects have been randomized into the study (ie, 60 subjects from Stage A of the study and the first 40 subjects from Stage B of the study). Further interim efficacy analyses will be conducted after each additional 50 MCI/Prodromal subjects have been randomized, to a maximum of 500 MCI/Prodromal subjects (ie, at 100, 150, 200, 250, 300, 350, 400, 450,

500 subjects randomized). If the study reaches full randomization, additional interim analyses will be conducted every 3 months until all subjects complete 18 months of treatment. The study will be monitored for futility at each interim analysis. Starting at the interim analysis for 200 subjects, the study will be monitored for success at each interim analysis. Each interim analysis will be conducted on data for the derived ADCOMS.

In addition, at each interim efficacy analysis, response adaptive randomization will be used to update the allocation of new subjects between placebo and active doses according to a predefined automated algorithm.

***The Mild AD Cohort***

A group sequential design will be used for the mild AD cohort. This design includes 3 looks, 2 interim looks (when 60% and 80% information fractions are achieved) and 1 final look. The information fraction is the number of assessments in all treatment arms divided by the total number of expected assessments. Interim analyses will be performed after the MCI/Prodromal cohort crosses the early success boundary. The corresponding efficacy boundaries will be 0.076, 0.022, and 0.0423 for the first, second, and final analyses, respectively. If the actual information fraction during the interim analyses is different from 60% or 80% at the interim, the efficacy boundaries will be adjusted based on the actual information fraction.

If early success in the MCI/Prodromal cohort is not achieved before the final analysis that is performed when all subjects have completed 18 months treatment, then only a final analysis will be performed in mild AD subjects. In the event of futility in the MCI/Prodromal cohort, an analysis will be performed for the mild AD cohort based on the data for mild AD subjects available at that time.

Randomization into the Mild AD cohort will remain at a fixed schedule throughout Stage B of the study.

The interim analyses in the Mild AD cohort will be conducted by an independent analysis group.

### 9.7.4 Other Statistical/Analytical Issues

**Adaptive Randomization in the MCI/Prodromal Cohort**

Randomization to placebo or 1 of 3 dose groups of E2609 will be fixed for the first 100 subjects randomized in the study (1:1:1:1; placebo to each of the 3 active doses). Randomization probabilities to each treatment group will be updated at each interim analysis, such that the randomization probability will be increased for the placebo group and dosage groups that represent the potential target dose ($ED_{90}$), and simultaneously decreased for other active arms.

Within the 2 clinical populations (MCI/Prodromal and mild AD), subjects will be stratified at randomization by *ApoE4* status (positive or negative) and prior treatment with AChEIs or memantine or both (yes or no).

Subjects with mild AD will be randomized to placebo or 1 of 2 dose groups of E2609.

### 9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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# 11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

## 11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

## 11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

## 11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

## 11.4 Recording of Data

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document, except when a section of the eCRF itself is used as the source document. Any correction to entries made on the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each eCRF. The investigator will report the eCRFs to the sponsor and retain a copy of the eCRFs.

## 11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents.

## 11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

## 11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

## 11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

## 11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

## 11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or CTA executed between the institution/investigator and the sponsor/CRO.

## 11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

## 11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

# 12 APPENDICES

## Appendix 1 Sponsor's Grading for Laboratory Values

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **BLOOD/BONE MARROW** | | | | |
| Hemoglobin (conversion from g/dL×0.6206) | **Female** (ULN=15.9 g/dL)<br><11.1 – 10.0 g/dL<br><111 – 100 g/L<br><6.9 – 6.2 mmol/L<br>**Male** (ULN=17.7 g/dL)<br><12.6 – 10.0 g/dL<br><126 – 100 g/L<br><7.8 – 6.2 mmol/L | <10.0 – 8.0 g/dL<br><100 – 80 g/L<br><6.2 – 4.9 mmol/L | <8.0 g/dL<br><80 g/L<br><4.9 mmol/L;<br>transfusion indicated | life-threatening consequences; urgent intervention indicated |
| Leukocytes (total white blood cell) | <3.40 – 3.0×$10^9$/L<br><3.40 $10^3$/uL – 3000/$mm^3$<br>(ULN=10.80 $10^3$/µL) | <3.0 – 2.0×$10^9$/L<br><3000 – 2000/$mm^3$ | <2.0 – 1.0×$10^9$/L<br><2000 – 1000/$mm^3$ | <1.0×$10^9$/L<br><1000/$mm^3$ |
| Lymphocytes | < 0.70 $10^3$/uL – 800/$mm^3$<br><0.70 – 0.8×$10^9$/L<br>(ULN=3.10 $10^3$/µL) | <800 – 500/$mm^3$<br><0.8 – 0.5×$10^9$/L | <500 – 200/$mm^3$<br><0.5 – 0.2×$10^9$/L | <200/$mm^3$<br><0.2×$10^9$/L |
| Neutrophils | <1.40– 1.5×$10^9$/L<br><1.40 $10^3$/uL – 1500/$mm^3$<br>(ULN=7.00 $10^3$/µL) | <1.5 – 1.0×$10^9$/L<br><1500 – 1000/$mm^3$ | <1.0 – 0.5×$10^9$/L<br><1000 – 500/$mm^3$ | <0.5×$10^9$/L<br><500/$mm^3$ |
| Platelets | <155 – 75.0×$10^9$/L<br><155 $10^3$/uL – 75,000/$mm^3$<br>(ULN=379 $10^3$/µL) | <75.0 – 50.0×$10^9$/L<br><75,000 – 50,000/$mm^3$ | <50.0 – 25.0×$10^9$/L<br><50,000 – 25,000/$mm^3$ | <25.0×$10^9$/L<br><25,000/$mm^3$ |
| **METABOLIC/LABORATORY** | | | | |
| Albumin, serum- low (hypoalbuminemia) | **2 - 59 years** (ULN=5.5 g/dL)<br><3.5 – 3 g/dL<br><35 – 30 g/L<br>**59 -69 years** (LLN-ULN)<br>3.6 g/dL – 4.8 g/dL<br>**69 -79 years** (LLN-ULN)<br>3.5g/dL – 4.8g/dL<br>**79 -89 years** (LLN-ULN)<br>3.5g/dL – 4.7g/dL<br>**89 -150 years** (LLN-ULN)<br>3.2g/dL – 4.6g/dL | <3 – 2 g/dL<br><30 – 20 g/L | <2 g/dL<br><20 g/L | life-threatening consequences; urgent intervention indicated |
| Alkaline phosphatase | **Female:**<br>**18 -19 years**<br>>101 – 3.0×101<br>**19 -61 years**<br>ULN=107<br>**61 -71 years**<br>ULN=112<br>**71 -150 years**<br>ULN=108<br>**Male**<br>**18 -19 years**<br>>127 – 3.0×127<br>**19 -61 years**<br>ULN=102<br>**61 -71 years**<br>ULN=103<br>**71 -150 years**<br>ULN=105 | >3.0 – 5.0×ULN<br>See previous column for ULN values | >5.0 – 20.0×ULN<br>See previous column for ULN values | >20.0×ULN<br>See previous column for ULN values |
| Alanine aminotransferase | **Female:**<br>>32 – 3.0×32<br>**Male:**<br>>44 – 3.0 x 44 | **Female:**<br>>3.0 – 5.0×32<br>**Male**<br>>3.0 – 5.0×44 | **Female:**<br>>5.0 – 20.0×32<br>**Male:**<br>>5.0 – 20.0×44 | **Female:**<br>>20.0×32<br>**Male:**<br>>20.0×44 |
| Aspartate aminotransferase | >40 – 3.0×40 | >3.0 – 5.0×40 | >5.0 – 20.0×40 | >20.0×40 |

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Bilirubin (hyperbilirubinemia) | >1.2 – 1.5×1.2 | >1.5 – 3.0×1.2 | >3.0 – 10.0×1.2 | >10.0×1.2 |
| Calcium, serum-low (hypocalcemia) (conversion to mmol×0.25) | <8.5 – 8.0 mg/dL<br><2.13 – 2.0 mmol/L | <8.0 – 7.0 mg/dL<br><2.0 – 1.75 mmol/L | <7.0 – 6.0 mg/dL<br><1.75 – 1.5 mmol/L | <6.0 mg/dL<br><1.5 mmol/L |
| Calcium, serum-high (hypercalcemia) | >10.6 – 11.5 mg/dL<br>>2.65 – 2.9 mmol/L | >11.5 – 12.5 mg/dL<br>>2.9 – 3.1 mmol/L | >12.5 – 13.5 mg/dL<br>>3.1 – 3.4 mmol/L | >13.5 mg/dL<br>>3.4 mmol/L |
| Cholesterol, serum-high (hypercholesterolemia) (conversion to mmol/L ×0.02586) | **0 -19 years**<br>>169 – 300 mg/dL<br>>4.37 – 7.75 mmol/L<br>**19 -150 years**<br>>199 – 300 mg/dL<br>>5.15 – 7.75 mmol/L | >300 – 400 mg/dL<br>>7.75 – 10.34 mmol/L | >400 – 500 mg/dL<br>>10.34 – 12.92 mmol/L | >500 mg/dL<br>>12.92 mmol/L |
| Creatinine | **Female**<br>>1.00 mg/dL – 1.5×1.00<br>**Male**<br>>1.27 mg/dL – 1.5×1.27 | **Female**<br>>1.5 – 3.0×1.00<br>**Male**<br>>1.5 mg/dL – 3.0×1.27 | **Female**<br>>3.0 – 6.0×1.00<br>**Male**<br>>1.5 mg/dL – 3.0×1.27 | **Female**<br>>6.0×1.00<br>**Male**<br>>1.5 mg/dL-3.0×1.27 |
| Gamma glutamyl transpeptidase | **Female**<br>>60 IU/L – 3.0×60<br>**Male**<br>>65 IU/L – 3.0×65 | **Female**<br>>3.0 – 5.0×60<br>**Male**<br>>3.0 – 5.0×65 | **Female**<br>>5.0 – 20.0×60<br>**Male**<br>>5.0 – 20.0×65 | **Female**<br>>20.0×60<br>**Male**<br>>20.0×65 |
| Glucose, serum-high (hyperglycemia) (conversion to mmol/L ×0.0555) | **Fasting glucose value**<br>>99 – 160 mg/dL<br>>5.5 – 8.9 mmol/L | **Fasting glucose value**<br>>160 – 250 mg/dL<br>>8.9 – 13.9 mmol/L | >250 – 500 mg/dL;<br>>13.9 – 27.8 mmol/L;<br>hospitalization indicated | >500 mg/dL;<br>>27.8 mmol/L;<br>life-threatening consequences |
| Glucose, serum-low (hypoglycemia) | <65 – 55 mg/dL<br><3.6 – 3.0 mmol/L | <55 – 40 mg/dL<br><3.0 – 2.2 mmol/L | <40 – 30 mg/dL<br><2.2 – 1.7 mmol/L | <30 mg/dL<br><1.7 mmol/L<br>life-threatening consequences;<br>seizures |
| Phosphate, serum-low (hypophosphatemia) (conversion to mmol/L ×0.323) | <2.5 – 2.5 mg/dL<br><0.81 – 0.8 mmol/L | <2.5 – 2.0 mg/dL<br><0.8 – 0.6 mmol/L | <2.0 – 1.0 mg/dL<br><0.6 – 0.3 mmol/L | <1.0 mg/dL<br><0.3 mmol/L<br>life-threatening consequences |
| Potassium, serum-high (hyperkalemia) | >5.5 – 5.5 mmol/L | >5.5 – 6.0 mmol/L | >6.0 – 7.0 mmol/L<br>hospitalization indicated | >7.0 mmol/L<br>life-threatening consequences |
| Potassium, serum-low (hypokalemia) | <3.5 mEq/L – 3.0 mmol/L | <LLN – 3.0 mmol/L;<br>symptomatic; intervention indicated | <3.0 – 2.5 mmol/L<br>hospitalization indicated | <2.5 mmol/L<br>life-threatening consequences |
| Sodium, serum-high (hypernatremia) | >144 mEq/L – 150 mmol/L | >150 – 155 mmol/L | >155 – 160 mmol/L<br>hospitalization indicated | >160 mmol/L<br>life-threatening consequences |
| Sodium, serum-low (hyponatremia) | <134 mEq/L – 130 mmol/L | Not applicable | <130 – 120 mmol/L | <120 mmol/L<br>life-threatening consequences |
| Triglyceride, serum-high (hypertriglyceridemia) | 150 – 300 mg/dL<br>1.71 – 3.42 mmol/L | >300 – 500 mg/dL<br>>3.42 – 5.7 mmol/L | >500 – 1000 mg/dL<br>>5.7 – 11.4 mmol/L | >1000 mg/dL<br>>11.4 mmol/L<br>life-threatening consequences |
| Uric acid, serum-high (hyperuricemia) | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | Not applicable | **Female**<br>>7.1 – 10 mg/dL<br>**Male**<br>>8.6 – 10 mg/dL<br>**Both**<br>≤0.59 mmol/L without physiologic consequences | >10 mg/dL<br>>0.59 mmol/L<br>life-threatening consequences |

LLN = lower limit of normal, ULN = upper limit of normal.

# Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, Listing 3, Listing 4, and Listing 5. Medications permitted with restrictions are listed in Listing 6, Listing 7, and Listing 8. **These may not be all-inclusive listings.** Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-202 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 8 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

## Prohibited Prior/Concomitant Medications

### Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Prohibited from 14 days (or 5 half-lives, whichever is longer) before Baseline until after the last treatment visit** | | |
| **Anti-arrhythmic/ abnormal heart rhythm** | | |
| Amiodarone | Cordarone; Pacerone | Incidence in females greater than males, Torsades de Pointes risk regarded as low |
| Disopyramide | Norpace | Incidence in females greater than males |
| Dofetillide | Tikosyn | |
| Ibutilide | Corvert | Incidence in females greater than males |
| Procainamide | Pronestyl; Procan | |
| Quinidine | Cardioquin; Quinaglute | Incidence in females greater than males |
| Sotalol | Betapace | Incidence in females greater than males |
| **Antihistamine/ allergic rhinitis** | | |
| Astemizole | Hismanal | No longer available in United States |
| Terfenadine | Seldane | No longer available in United States |
| **Anti-anginal/ heart pain** | | |
| Bepridil | Vascor | Incidence in females greater than males |
| **Antibiotic/ bacterial infection** | | |
| Clarithromycin | Blaxin | |
| Moxifloxacin | Avelox | |
| Sparfloxadin | Zagam | |

## Listing 1 Drugs with High Risk of Torsades de Pointes or QTc Prolongation

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) | Comments |
|---|---|---|
| **Listing 1 continued** | | |
| **Antimalarial/ malaria infection** | | |
| Chloroquine | Aralen | |
| Halofantrine | Halfan | Incidence in females greater than males |
| **Antipsychotic/ anti-emetic/ schizophrenia/ nausea** | | |
| Chloropromazine | Thorazine | |
| **Gastrointestinal stimulant/ heartburn** | | |
| Cisapride | Propulsid | |
| **Antinausea/ nausea** | | |
| Domperidone | Motillum | Not available in the United States |
| **Sedative; antinausea/ anesthesia adjunct, nausea** | | |
| Droperidol | Inapsine | |
| **Antibiotic; gastrointestinal stimulant/ bacterial infection; increase gastrointestinal motility** | | |
| Erythromycin | Erythrocin; E.E.S. | Incidence in females greater than males |
| **Antipsychotic/ schizophrenia** | | |
| Haloperidol | Haldol | When given intravenously or at higher than recommended doses, risk of sudden death, QT prolongation, and torsades increases |
| Mesoridazine | Serentil | |
| Thioridazine | Mellaril | |
| **Opiate agonist/ pain control, narcotic dependence** | | |
| Levomethadyl | Orlaam | |
| Methadone | Methadose; Dolophine | Incidence in females greater than males |
| **Anti-infective/ pneumocystis pneumonia** | | |
| Pentamidine | Pentam; NebuPent | Incidence in females greater than males |
| **Antipsychotic/ Tourette's tics** | | |
| Pimozide | Orap | Incidence in females greater than males |
| **Antilipemic/ hypercholesterolemia** | | |
| Probucol | Lorelco | No longer available in United States |
| **Anticancer** | | |
| Arsenic trioxide | Trisenox | Used for leukemia |
| Vandetanib | Zactima | Used for thyroid cancer |

Note: This list is not exhaustive.

QTc = Corrected QT interval.

## Listing 2 Prohibited Medications Within 7 Days (or 5 Half-lives, Whichever is Longer) Before Baseline Until After the Last Treatment Visit)

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Anticoagulants** | |
| Warfarin | Coumadin, Jantoven |
| Dicumarol | Dicumarol |
| Dabigatran | Pradaxa |
| Enoxaparin | Lovenox |
| Dalteparin | Fragmin |
| Anisindione | Miradon |
| Danaparoid | Orgaran |
| Pentosan polysulfate sodium | Elmiron |
| Tinzaparin | Innohep |
| Adeporin | Normiflo |
| Heparin Sodium | Monoject |
| Bivalirudin | Angiomax |
| Argatroban | Argatroban |
| Lepirudin | Refludan |
| Fondaparinux | Arixtra |
| Antithrombin III | ATryn, Thrombate III |
| Streptokinase | Streptase |
| Lanoteplase | Lanoplase |
| Reteplase | Retavase, Retevase |
| Staphylokinase | Eskinase, Heberkinasa Kabikinase, Streptase, Thrombosolv, Zykinase |
| Tenecteplase | TNKase |
| Urokinase | Abbokinase, Kinlytic |
| Alteplase, tPA | Activase, Cathflo Activase |
| **Antiplatelet drugs** | |
| Aspirin and Plavix (only in subjects undertaking lumbar puncture in biomarker subgroup) | Aspirin or clopidogrel is permitted in all subjects. Aspirin and clopidogrel in combination is permitted in subjects who are not to undergo lumbar puncture. |

Note: This list is not exhaustive.

## Listing 3 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline Until After the Last Treatment Visit

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Systemic Immunosuppressants[a] and Immunomodulatory therapy** | |
| Prednisolone | Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS |
| Methylprednisolone | Medrol, Meprolone |
| Dexamethasone | Decadron, Dexasone, Diodex, Hexadrol, Maxidex |
| Azathioprine | Azasan, Imur |
| Mycophenolate | CellCept, Myfortic |
| Fingolimod | Gilenya |
| Methotrexate | Trexall |
| Ciclosporine | Gengraf, Neoral |

Note: This list is not exhaustive.

a: Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

## Listing 4 Prohibited Medications Within 6 months before randomization

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Immunoglobulin therapy** | |
| Ranibizumab | Lucentis |
| Bevacizumab | Avastin |
| Infliximab | Remicade |
| Etanercept | Enbrel |
| Adalimumab | Humira |
| Omalizumab | Xolair |
| Efalizumab | Raptiva |
| Immune globulin IV, IVIG, IGIV | Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S |
| Other monoclonal antibodies not listed here | |

Note: This list is not exhaustive.

## Listing 5 Prohibited Live Vaccines Within 3 Months Before Randomization Until After the Last Treatment Visit (this does not apply to non-live/inactivated vaccines)

| **Bacterial vaccines** | **Viral vaccines** |
|---|---|
| Bacillus Calmette-Guérin vaccine against tuberculosis | Measles vaccination |
| Typhoid vaccination (oral) | Mumps vaccination |
| Cholera vaccination (oral) | Rubella vaccination |
| | Oral polio vaccination (Sabin) |
| | Yellow fever vaccination |
| | Varicella (chickenpox) vaccination |
| | Rotavirus vaccination |
| | Japanese encephalitis vaccination |
| | Live attenuated influenza vaccine (FluMist, Fluenz) |

This list is not exhaustive

## Permitted Prior/Concomitant Medications

### Listing 6 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Baseline Cognitive Assessments at Visit 2 and Remain on the Same Stable Dose from Baseline to Follow Up Visit 2

| **Generic name** | **Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™)** |
|---|---|
| **Cognitive Enhancers** | |
| Donepezil | Aricept |
| Rivastigmine | Exelon |
| Galantamine | Reminyl |
| Memantine | Nemanda |

Note: This list is not exhaustive.

## Listing 7 Permitted medications used on PRN basis which are not to be used within 72 hours before cognitive testing

| Generic name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Opiates** | |
| Morphine | Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol |
| **Opiate Agonists** | |
| Meperidine | Demerol, Meperitab |
| Fentanyl | Actiq, Duragesic, Fentora, Onsolis, Sublimaze |
| Codeine | Codeine |
| Oxycodone | Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol |
| Other opioids or opioid agonists which are used on PRN basis | |
| **Benzodiazepines and sedatives** | |
| Estazolam | ProSom |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Triazolam | Halcion |
| Midazolam | Versed |
| Lorazepam | Ativan |
| Flunitrazepam | Rohypnol |
| Temazepam | Restoril |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Chlordiazepoxide | H-Tran, Librium |
| Flurazepam | Dalmane |
| Zopiclone | (various) |
| Zolpidem | Ambien; others |
| Ramelteon | Rozerem |
| Amitriptyline | (various) |
| Dothiepin | (various) |
| Risperidone | Risperdal |
| Olanzapine | Zyprexa |
| Promethazine | Phenergan; others |
| Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives | |

This list is not exhaustive

PRN = Pro re nata

## Listing 8 Permitted Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| If to be used on a PRN basis see Listing 7. If to be used chronically, subjects must be on a stable dose for ≥4 weeks before Baseline. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks. | |
| **Antidepressants** | |
| Bupropion | Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin |
| Nefazodone | Serzone |
| Rasagiline | Azilect |
| Selegiline | EMSAM |
| Isocarboxazid | Marplan |
| Phenelzine | Nardil |
| Tranylcypromine | Parnate |
| Citalopram | Celexa |
| Fluvoxamine | Luvox |
| Escitalopram | Lexapro |
| Paroxetine | Paxil, Pexeva |
| Fluoxetine | Prozac, Sarafem, Selfemra |
| Sertraline | Sertaraline, Zoloft |
| Duloxetine | Cymbalta |
| Venlafaxine hydrochloride | Effexor |
| Desvenlafaxine | Pristiq |
| Amitriptyline hydrochloride | Elavil |
| Clomipramine hydrochloride | Anafranil |
| Desipramine hydrochloride | Norpramin |
| Doxepin hydrochloride | Prudoxin, Silenor, Sinequan, Zonalon |
| Imipramine hydrochloride | Tofranil |
| Nortriptyline hydrochloride | Aventyl, Pamelor |
| Trimipramine maleate | Surmontil |
| Protriptyline hydrochloride | Vivactil |
| Amoxapine | Amoxapine |
| Trazodone hydrochloride | Desyrel, Oleptro |
| Maprotiline hydrochloride | Ludiomil |
| Mirtazapine | Remeron Soltab |

## Listing 8 Permitted Medications

| Generic Name | Brand name (Names shown are not exhaustive and are examples only; names may be the ® or ™) |
|---|---|
| **Mood Stabilizers (Listing 8 continued)** | |
| Carbamazepine | Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR |
| Lamotrigine | Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR |
| Valproic acid | Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate |
| **Antipsychotics** | |
| Acetophenazine | Tindal |
| Aripiprazole | Abilify |
| Asenapine | Saphris |
| Olanzapine | Zyprexa |
| Chlorpromazine | Thorazine |
| Haloperidol | Haloperidol, Haldol |
| Clozapine | Clozaril, Fazaclo |
| Fluphenazine | Prolixin |
| L-Methylfolate | Deplin, L-Methylfolate Calcium |
| Loxapine | Loxitane |
| Mesoridazine | Serentil |
| Perphenazine | Trilafon |
| Quetiapine | Seroquel |
| Risperidone | Risperdal |
| Thioridazine | Mellaril |
| Thiothixene | Navane |
| Trifluoperazine | Stelazine |
| **Benzodiazepines** | |
| Estazolam | ProSom |
| Alprazolam | Alprazolam Intensol, Niravam, Xanax |
| Triazolam | Halcion |
| Midazolam | Versed |
| Lorazepam | Ativan |
| Flunitrazepam | Rohypnol |
| Temazepam | Restoril |
| Clonazepam | Ceberclon, Klonopin |
| Diazepam | Diastat, Dizac, Valium |
| Chlordiazepoxide | H-Tran, Librium |
| Flurazepam | Dalmane |
| Zopiclone | Imovane, Zimovane |
| Zopidem | Ambien, Ambien CR, Intermezzo, Stilnox, Stilnoct, Sublinox, Hypnogen, Zolsana |

Note: This list is not exhaustive.
PRN = Pro re nata

# Appendix 3 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

## Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

## Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

### Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

### Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

# PROTOCOL SIGNATURE PAGE

**Study Protocol Number:** E2609-G000-202
**Study Protocol Title:** A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof of Concept, Dose-Finding Study To Evaluate Safety, Tolerability and Efficacy of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's Disease
**Investigational Product Name:** E2609
**IND Number:** 109308
**EudraCT Number:** 2014-002723-94

**SIGNATURES**
Authors:

PPD

PPD Neuroscience and General Medicine Product Creation Unit
Eisai Ltd.

Date

PPD

PPD Neuroscience and General Medicine Product Creation Unit
Eisai Ltd.

Date

PPD

Neuroscience and General Medicine Product Creation Unit
Eisai Inc.

Date

# INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
| **Study Protocol Number:** | E2609-G000-202 |
| **Study Protocol Title:** | A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Proof of Concept, Dose-Finding Study To Evaluate Safety, Tolerability and Efficacy of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's Disease |
| **Investigational Product Name:** | E2609 |
| **IND Number:** | 109308 |
| **EudraCT Number:** | 2014-002723-94 |

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

| Investigator | Signature | Date |
|---|---|---|