REVISION HISTORY

Revisions to Version 5.0 **New version/date: Version 6.0/03 Jan 2020 (per Amendment 05)**		
Change	**Rationale**	**Affected Protocol Sections**
Added results of nonclinical toxicology study.	New nonclinical toxicology findings	Section 7.1.1.3 Section 7.2.2
Added requirement for males subjects to use highly effective contraception and requirement to report pregnancy in female partners of male subjects.	New nonclinical toxicology findings	Section 9.4.7.3 Section 9.5.4.2 Section 9.5.5
Revised the order of the secondary efficacy endpoints.	To enable the secondary endpoints to be part of the statistical hierarchy of testing so that this study can be used in the NDA as one of the pivotal studies	Synopsis • Objectives • Study Endpoints Section 8.2 Section 9.7.1.1.2

Revisions to Version 4.0 **New version/date: Version 5.0/03 Sep 2019 (per Amendment 04)**		
Change	**Rationale**	**Affected Protocol Sections**
Specified the percentage of randomized subjects who will be on memantine.	To comply with the EU Voluntary Harmonisation Procedure requirement for approval	Synopsis • Study Design Section 7.2.1 Section 9.1

Revisions to Version 3.0 **New version/date: Version 4.0/10 Jul 2019 (per Amendment 03)**		
Change	**Rationale**	**Affected Protocol Sections**
Removed restriction on the use of memantine prior to and during study participation.	Use of memantine is increasingly more common in patients with dementia with Lewy bodies (DLB) based on ongoing surveys with investigators, and it is also explicitly cited in some national treatment guidelines for DLB (eg, UK National Institute for Health and Care Excellence [2018]).	Synopsis • Study Design • Inclusion Criteria • Concomitant Drug/Therapy • Statistical Methods – Efficacy Analyses Section 7.1.1 Section 7.2.1 Section 9.1 Section 9.2 Section 9.3.1 Section 9.4.7.2 Section 9.5.1.2.1 Section 9.5.5 Section 9.7.1.4 Section 9.7.1.6.1 Section 9.7.1.8.2 Section 10
Removed ad hoc futility analysis	This was always considered optional and only to be performed if necessary. Moreover, ongoing review of variability data in the efficacy endpoints indicated that such a futility analysis would have high risk of a false negative conclusion on efficacy. Therefore, it will not be conducted.	Synopsis • Interim Analyses Section 9.7.3
Increased number of sites from 60 to 70	Due to the screen failure rate being higher than expected and some sites having exhausted their pool of subjects for enrollment, more new sites, to replace sites planned for closure are required.	Synopsis • Sites Section 6 Section 9.3

Revisions to Version 2.0 **New version/date: Version 3.0/15 Jun 2018 (per Amendment 02)**		
Change	**Rationale**	**Affected Protocol Sections**
Specified secondary endpoints for safety and tolerability	To specify measurable endpoints for safety and tolerability	• Synopsis: • Secondary Endpoints • Section 9.7.1.1.2
Add Section headings 7.2.1 and 7.2.2	7.2.1: Correction for clarity 7.2.2: To add Risk-Benefit Summary for completeness	• Section 7.2.1 • Section 7.2.2
Updated information regarding breaking of blind	Correction	• Section 9.4.6
Added “Capacity Rule”	To comply with feedback from Health Authorities	• Synopsis • Inclusion criteria • Section 5.3 • Section 9.3.1 • Section 9.5.5
Updated completion/discontinuation information	To add safety criteria	• Section 9.5.5
Added cerebrospinal fluid (CSF) substudy criteria and description	To provide all procedures specific for the optional CSF substudy in one location in the protocol	• Appendix 4

Revisions to Version 1.0 **New version/date: Version 2.0/30 Mar 2018 (per Amendment 01)**		
Change	**Rationale**	**Affected Protocol Sections**
Additional specification for implementation of Inclusion Criterion 2	Restricts enrollment to subjects who do not need new nuclear scan in countries where additional central regulatory review of radiation exposure is required. When such approval is granted, enrollment restriction is removed.	Synopsis, Inclusion Criteria Section 9.3.1
Updated estimated blood volume collected during the study	Alignment with Schedule of Procedures	Section 9.5.2.2, Table 7
Heart rate was changed to pulse when describing vital signs	Company convention	Section 9.5.1.5.5
Updated Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) to include number of items, categories, and correct scoring	Correction	Synopsis, Safety Assessments Section 9.5.1.5.8
Specified time for vital signs to align with approximate t_{max} time window at specific visits	As recommended by Japanese PMDA	Section 9.5.2.1, Table 6
Recommended subjects to avoid prolonged exposure to the sun or exposure to artificial ultra-violet light	As recommended by Japanese PMDA	Section 9.4.7.3
Removed criterion for pulse increase in the definition of orthostatic hypotension	As recommended by Japanese PMDA and for consistency with the literature	Section 9.5.1.5.5

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2027-G000-201
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Study To Evaluate the Efficacy, Safety and Tolerability of E2027 in Subjects With Dementia With Lewy Bodies
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 US Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 JP
Investigational Product Name:	E2027
Indication:	Subjects with dementia with Lewy bodies
Phase:	2
Approval Date:	V1.0 29 Jan 2018 (original protocol) V2.0 30 Mar 2018 (Amendment 01) V3.0 15 Jun 2018 (Amendment 02) V4.0 10 Jul 2019 (Amendment 03) V5.0 03 Sep 2019 (Amendment 04) V6.0 03 Jan 2020 (Amendment 05)
IND Number:	123614
EudraCT Number:	2017-003728-64
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 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.: E2027

Name of Active Ingredient: 7-(2-Methoxy-3,5-dimethylpyridin-4-yl)-1-[(3S)-tetrahydrofuran-3-yl]-1,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one maleate (International Union of Pure and Applied Chemistry [IUPAC])

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Study To Evaluate the Efficacy, Safety and Tolerability of E2027 in Subjects With Dementia With Lewy Bodies

Investigators

Investigators in North America, Europe and Japan

Sites

Approximately 70 sites in North America, Europe, and Japan (revised per Amendment 03)

Study Period and Phase of Development

Approximately 22 weeks for each subject.

Approximately 20 months for the study.

Phase 2

Objectives

Primary Objectives

- To determine whether E2027 is superior to placebo on the cognitive endpoint of Montreal Cognitive Assessment (MoCA) in subjects with dementia with Lewy bodies (DLB) after 12 weeks of treatment
- To determine whether E2027 is superior to placebo on the global clinical endpoint of Clinician's Interview Based Impression of Change Plus Caregiver Input (CIBIC-Plus) after 12 weeks of treatment

Secondary Objectives
(Order revised per Amendment 05)

- To determine whether E2027 is superior to placebo on the following secondary endpoints after 12 weeks of treatment:
  - Clinician Global Impression of Change in Dementia with Lewy Bodies (CGIC-DLB)
  - Cognitive Fluctuation Inventory (CFI)
  - Mini-Mental State Examination (MMSE)
  - Neuropsychiatric Inventory (NPI)
- To evaluate the safety and tolerability of E2027 in subjects with DLB
- To characterize the population pharmacokinetics (PPK) of E2027 in subjects with DLB, including evaluation of the effects of intrinsic and extrinsic factors on E2027 pharmacokinetics (PK)

Exploratory Objectives

- To explore the efficacy of E2027 compared to placebo on the following endpoints after 12 weeks of treatment:
  - Scales for Outcome in Parkinson's disease-Sleep (SCOPA-Sleep)
  - Dementia-related quality of life as assessed by the Dementia Quality of Life Measure (DEMQOL; interview of subject) and Dementia Quality of Life Measure by Proxy (DEMQOL-Proxy; interview of caregiver or informant about subject)
  - General health status as assessed by the EuroQol- 5 Dimension questionnaire (EQ-5D; completed by subject) and EuroQol- 5 Dimensions questionnaire by Proxy Version 1 (EQ-5D Proxy; caregiver or informant completion of report about subject)
- To evaluate the relationship between PK exposure of E2027 and its effects on various efficacy and safety endpoints
- To explore the PK/pharmacodynamic (PD) relationship between the exposure of E2027 in cerebrospinal fluid (CSF)/plasma and its effects on CSF PD biomarker endpoints, including CSF cyclic guanosine monophosphate (cGMP), if data permit
- To explore the relationship between the E2027 PD effects (including CSF cGMP) with E2027 effects on various efficacy endpoints, if data permit
- To explore collected pharmacogenomic (PGx) samples by investigating heterogeneity in clinical features of disease, including differences in baseline characteristics as well as response to compound (efficacy, safety and/or absorption, distribution, metabolism, and excretion [ADME]). These exploratory analyses are not limited to this protocol or project. These findings may be used for identification and validation of new drug targets.

Study Design

This is a multicentre, randomized, double-blind, placebo-controlled, parallel-group study in subjects with DLB who will be treated with placebo or E2027 (50 mg once daily [QD]) for 12 weeks.

In some of the countries selected for this study, donepezil is approved for DLB, with acetylcholinesterase inhibitors (AChEIs) and increasingly memantine often used as part of standard care in patients with DLB. Therefore, the study design allows for add-on therapy to standard of care for DLB, which includes AChEI and/or memantine at stable doses, except for any prohibited medications specified in this protocol. Subjects who are not receiving AChEI or memantine are also eligible, but are not permitted to start such medications during the study. (revised per Amendment 03) Randomization will be stratified based on whether subjects are on a stabilized dose of AChEI or not and by geographical region (ie, North America, Europe, or Japan). Up to approximately 20% of randomized subjects will be on memantine. (revised per Amendment 04) Subjects will be randomly assigned to placebo or E2027 (50 mg QD) in a ratio of 1:1.

For all subjects, study participation will comprise 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last for up to 6 weeks and will include a Screening Period (up to 5 weeks) and a Baseline Period (1 week). The Randomization Phase will last for 16 weeks and will include a Treatment Period (12 weeks) and a Follow-up Period (4 weeks).

Screening will occur between Day -42 and Day -8. 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 before the conduct of any screening procedures or assessments. All subjects will be assessed for eligibility through review of medical history, physical examination (including neurological examination), laboratory tests, vital signs and electrocardiograms (ECGs). They will be assessed on clinical scales of cognition and depression,

safety magnetic resonance imaging (MRI) of the brain and dopamine transporter (DAT) brain imaging or myocardial scintigraphy ([^{123}I]meta-iodobenzylguanidine [MIBG]) (if indicated in individual subjects and not previously performed) to confirm that they meet the diagnostic criteria and severity for DLB. Their motor features will be assessed on the Movement Disorders Society (MDS) Unified Parkinson's Disease Rating Scale Part III: Motor Examination (UPDRS-III) and staged by the Hoehn and Yahr Scale (HYS). Their history of suicidality will be assessed by the Columbia Suicide Severity Rating Scale (C-SSRS). They will also be assessed regarding other medical conditions and concomitant medications to ensure that these are stable with no changes to treatment required and that they do not interfere with their safety or study procedures.

Eligibility assessments at Screening will be conducted in tiers and subjects will need to satisfy eligibility criteria in each tier before proceeding to the next tier. In Tier 1 demographics, medical history (including history of DLB and other medical conditions) and concomitant medications will be reviewed. In Tier 2, clinical assessments on cognition and depression will be conducted in the morning (whenever possible) in subjects in the following order: MMSE and Geriatric Depression Scale (GDS) should be done first, followed by the MoCA and SCOPA-Sleep. The caregivers or informants will also complete the Short Fluctuation Questionnaire (SFQ), CFI, and the NPI. If the eligibility criteria regarding the MMSE and GDS are not met, the other procedures (MoCA, SCOPA-Sleep, SFQ, CFI, and NPI) do not have to be performed and the subject should be screen failed. In Tier 3 subjects will be assessed with the Modified Hachinski Ischemic Scale, UPDRS-III, HYS, and C-SSRS. In Tier 4 subjects will undertake physical examination, vital signs, ECG, and clinical laboratory tests. In Tier 5, subjects will be assessed by safety MRI for brain abnormalities that may affect eligibility. In Tier 6, if indicated as judged by the investigator, individual subjects may also undertake DAT brain imaging scan or myocardial MIBG scan to help establish their diagnosis. It is recommended that where appropriate Tiers 1 to 4 should be performed on the same day and Tiers 5 and 6 on a separate day. However, the investigator may perform the various tiers on separate days as appropriate for each subject. The scores of various clinical scales (including NPI, SFQ, and UPDRS-III) and cognitive tests (MMSE, MoCA) at Screening will be reviewed by a central process. Subjects who are diagnosed by the investigator with DLB but whose scores on clinical scales or cognitive tests are found not to be consistent with the diagnosis during central review will be discussed with the investigator to determine their eligibility.

Due to the intrinsic variability of cognitive functions in DLB, subjects who screen fail at Tier 2 may be rescreened after at least 30 days, but as a guide, rescreening frequency should not be more frequent than once every 4 months and a subject should not be rescreened more than 2 times under the same version of the eligibility criteria. Subjects who are deemed eligible after passing all tiers at Screening will proceed to the Baseline Visit.

The baseline visit may take place at any time up to 7 days before the first dose of study drug (Day 1, ie, during Day -7 to Day -1, but should take place at least 2 weeks after the Screening Visit Tier 2 assessments). In subjects who had DAT brain imaging scan or MIBG myocardial scan during Screening, the Baseline Visit should take place at least 1 week after the scan. Study assessments should be conducted in the morning (whenever possible). Cognition will be assessed by the MoCA, which must be the first clinical scale to be administered before any invasive procedures. It is recommended that after the MoCA the following efficacy assessments in subjects should be performed in the following overall order (other study assessments may be conducted in between these efficacy assessments): CIBIS-Plus and SCOPA-Sleep. The subject will be interviewed to complete the DEMQOL. The EQ-5D will be self-administered and completed by the subject. The caregiver or informant will also complete the CIBIS-Plus, NPI, CFI, EQ-5D Proxy and will be interviewed to complete the DEMQOL-Proxy. The rater administering the CIBIS-Plus should be independent of the rater(s) who administer the other clinical scales.

At Baseline Visit subjects will be assessed regarding other medical conditions and concomitant medications (including medications for DLB) to ensure that these remain stable with no changes to treatment required and that they do not interfere with their safety or study procedures. Other safety assessment including vital signs, ECGs, laboratory tests, and C-SSRS will also be conducted.

After completing study assessments at the Baseline Visit, subjects who continue to be eligible will proceed to the Randomization Phase, and will be randomly assigned to placebo or E2027 (50 mg QD). They will be provided with study drug (placebo or E2027) to start administration in the morning of Day 1 at home. They will continue to take study drug for 12 weeks. During the Treatment Period study visits will be conducted after 2, 4, 6, 9 and 12 weeks on study drug. Safety assessments will be conducted at all these visits. Efficacy assessments will be performed after 6 and 12 weeks on study drug and should be performed at approximately the same time of the day as at the Baseline Visit whenever possible (preferably in the morning). The MoCA should be the first clinical scale to be administered before any invasive procedures. Whenever possible, a subject should have the same rater administering the MoCA and the CIBIC-Plus throughout his/her participation in the study. It is recommended that other efficacy assessments in subjects should be performed in the following order (other study assessments may be conducted in between these efficacy assessments): CIBIC-Plus, MMSE (after 12 weeks only), and SCOPA-Sleep. The rater administering the CIBIC-Plus should be independent of the rater(s) who administer the other clinical scales. The subject will self-complete the EQ-5D. The caregiver or informant will also complete the CIBIC-Plus, NPI, CFI, and EQ-5D Proxy Version 1. In addition, at the study visit after 12 weeks on study drug interviews with the subject and the caregiver or informant will be conducted to complete the DEMQOL (subject) and DEMQOL-Proxy (caregiver or informant). Safety assessments will be conducted at these visits, including review of adverse events (AEs), vital signs, ECG, laboratory safety tests, C-SSRS, and UPDRS-III. The investigator will review all the efficacy endpoints and safety data at the visits after 6 weeks and 12 weeks on study drug and formulate the CGIC-DLB of the subject's clinical status from Baseline.

After the Treatment Period, subjects will complete a Follow-Up Visit 4 weeks after the final dose of study drug. Efficacy assessments should be performed at approximately the same time of the day as at the Baseline Visit whenever possible (preferably in the morning). The MoCA should be the first clinical scale to be administered before any invasive procedures. It is recommended that other efficacy assessments in subjects should be performed in the following order (other study assessments may be conducted in between these efficacy assessments): MMSE and SCOPA-Sleep. The caregiver or informant will also complete the CFI and NPI. Safety assessments will also be completed.

The end of study is defined as the last subject completing the Follow-Up Visit.

<u>Early Discontinuation</u>

Subjects who prematurely discontinue study drug for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their final dose of study drug. The safety and efficacy assessments normally performed after 12 weeks of treatment will be conducted at the ED Visit. In addition, subjects who discontinue study drug are expected to continue in the study for the originally scheduled visits, starting with next such visit that is >7 days after the ED Visit. Subjects who prematurely discontinue the study should attend at least 1 originally scheduled visit after the ED Visit.

CSF Substudy

A subset of subjects will participate in a substudy in which CSF will be collected by lumbar puncture (LP) during Screening and again during the Randomization Phase after 9 weeks of treatment on study drug. Participation in the substudy will be voluntary. After they have completed all screening assessments and are deemed eligible for the study, a baseline CSF sample will be collected at least 7 days before the Baseline Visit. If necessary, in these subjects the Screening Period may be extended by 1 week after discussion with the sponsor medical monitor. After they have completed 9 weeks of treatment, they will have a 2nd CSF sample collected. The CSF samples will be collected in the morning at approximately the same time, either in the fasted state (preferred) or at least 2 hours after breakfast.

As data permit, CSF cGMP will be assayed to evaluate the PD effects of E2027 in these subjects with DLB. Other CSF PD biomarkers related to DLB or E2027 PD effects may also be assayed if appropriate. CSF E2027 concentrations will also be determined.

Data Safety Monitoring Board

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the study is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

Number of Subjects

Approximately 260 subjects will be screened to provide a maximum of 182 randomized subjects. Allowing for a 12% dropout rate, 160 randomized subjects are expected to complete the study.

Participation in the CSF substudy is voluntary. It is estimated that approximately 30% of subjects will participate in the CSF substudy.

Inclusion Criteria

1. Male or female, age 50 to 85 years, inclusive at time of consent.
2. Meet criteria for probable DLB (as defined by the 4th report of the DLB Consortium) (Appendix 1). Specific situations regarding the use the imaging are described below:
   a. have 1 core clinical feature only by the investigator and who did not have previous reports of DAT brain imaging scan, MIBG scan or polysomnography (PSG) will undertake DAT brain imaging scan or MIBG scan as organized by the investigator.
   b. have 2 or more core clinical features by the investigator but who are judged as having only 1 core clinical feature by central reviewer and who did not have previous reports of DAT brain imaging scan, MIBG scan or PSG may undertake DAT brain imaging scan or MIBG scan after discussion with the sponsor medical monitor.
   c. have 2 or more core clinical features by the investigator and the central reviewer and who did not have previous reports of DAT brain imaging scan, MIBG scan or PSG may undertake DAT brain imaging scan or MIBG scan after discussion with the sponsor medical monitor if the investigator considers that imaging is necessary to confirm the diagnosis.

   Where there are local/national regulatory requirements for additional central regulatory review of radiation exposure for the use of DAT / MIBG scans, enrollment of subjects is restricted to

those who do not require a new DAT / MIBG scan conducted under this study (ie, subjects who have historical DAT/MIBG scan/PSG results, or subjects who have 2 core clinical features of DLB) until such approval is granted by the regulatory authority on radiation exposure. Thereafter enrollment of subjects will extend to those who may require a new DAT / MIBG scan under this study. (revised per Amendment 01)

3. MMSE $\geq$14 and $\leq$26 at Screening Visit.
4. Has experienced visual hallucinations during the past 4 weeks before Screening Visit.
5. If receiving AChEIs, must have been on a stable dose for at least 12 weeks before Screening Visit, with no plans for dose adjustment during the study. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs from Screening to the end of the study.
6. If receiving memantine, must have been on a stable dose for at least 12 weeks before Screening Visit, with no plans for dose adjustment during the study. Treatment naïve subjects can be entered into the study but there should be no plans to initiate treatment with memantine from Screening to the end of the study. (revised per Amendment 03)
7. 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, not be suffering from cognitive impairment, be sufficiently familiar with the subject and 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 should normally be residing with 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. As a guide the caregiver or informant should have contact with the subject on at least 4 days a week and each day for a total of at least 5 hours. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At all visits caregivers or informants need to attend the visit in person along with the subject. If during the study, the designated caregiver or informant relinquishes his/her responsibilities as caregiver or informant, a replacement caregiver or informant who meets the criteria above and who has similar knowledge of the subject's clinical status from Baseline throughout the Treatment Period must be found. If no such replacement caregiver or informant is available, the subject must be discontinued from the study.
8. Provide written informed consent. If a subject lacks capacity to consent in the investigator's opinion, the subject's assent should be obtained, as required in accordance with local laws, regulations and customs, plus the written informed consent of a legal representative should be obtained (capacity to consent and definition of legal representative should be determined in accordance with applicable local laws and regulations). In countries where local laws, regulations, and customs do not permit subjects who lack capacity to consent to participate in this study, they will not be enrolled (revised per Amendment 02)

Exclusion Criteria

1. Any neurological condition that may be contributing to cognitive impairment above and beyond those caused by the subject's DLB, including any comorbidities detected by clinical assessment or MRI.
2. History of transient ischemic attacks or stroke within 12 months of Screening.

3. Modified Hachinski Ischemic Scale >4.
4. Parkinsonian (extrapyramidal) features with Hoehn & Yahr stage IV or higher.
5. Any major psychiatric diagnosis, including schizophrenia, bipolar disorder and current major depressive disorder as per Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V).
6. GDS score >8.
7. Severe visual or hearing impairment that may interfere with the subject study assessments including cognitive testing.
8. History of deep brain stimulation or other neurosurgical procedure for Parkinson's disease.
9. Have thyroid stimulating hormone (TSH) above 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 whether or not they are taking thyroid supplements.
10. Abnormally low serum Vitamin B12 levels (less than the lower limit of normal [LLN]) for the testing laboratory (if subject is taking Vitamin B12 injections, level should be at or above the LLN for the testing laboratory).
11. Contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or positron emission tomography (PET) scanning as per local guidelines need not be excluded.
12. Evidence of other clinically significant lesions that suggest a dementia diagnosis other than DLB on brain MRI at Screening. All MRIs will be acquired using a standardized procedure that will be outlined in the Imaging Charter and Imaging Acquisition Guidelines (IAG) and will be read by an approved centralized reader.
13. Other significant pathological findings on brain MRI at Screening, including but not limited to: any macrohemorrhage (greater than 10 mm at greatest diameter); an area of superficial siderosis; evidence of cerebral contusion, encephalomalacia, aneurysms, arteriovenous 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 or equal to 1 cm at their greatest diameter need not be exclusionary])
14. Hypersensitivity to E2027 or any of the excipients.
15. A prolonged corrected QT interval calculated using Fridericia's formula (QTcF) as demonstrated by triplicate ECG at the Screening or Baseline Visit (ie, mean value >450 msec).
16. Had symptomatic orthostatic hypotension or symptomatic orthostatic tachycardia which resulted in hospitalization or urgent medical review in hospital in the past 12 months before Screening.
17. Any other clinically significant abnormalities that in the opinion of the investigator, require further investigation or treatment or that may interfere with study procedures or safety in the following:
    - Physical examination, ECG, vital signs at Screening or Baseline Visit
    - Laboratory tests at Screening Visit

18. Malignant neoplasms within 3 years of Screening (except for basal or squamous cell carcinoma of the skin, or localized prostate cancer in male subjects). Subjects who had malignant neoplasms but who have had at least 3 years of documented uninterrupted remission before Screening need not be excluded.
19. Has a "yes" answer to C-SSRS suicidal ideation Type 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.
20. 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 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.
21. Any other medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) which are not stably and adequately controlled, or which in the opinion of the investigator may affect the subject's safety or interfere with the study assessments.
22. Taking any of the prohibited medications or not meeting the requirements regarding stable doses of permitted medications.
23. Participation in a clinical study involving any investigational drug/device for DLB within 6 months before Screening or any other investigational drug/device in the 8 weeks or 5 half-lives (whichever is longer) of the study medication before Screening unless it can be documented that the subject was in a placebo treatment arm.
24. Planned surgery which requires general, spinal or epidural anesthesia that will take place during the study. Planned surgery that requires only local anesthesia and can be undertaken as a day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.
25. Females who are breastfeeding or pregnant at Screening or Baseline (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). 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.
26. Females of childbearing potential.
    (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]).
27. For subjects who participate in the CSF substudy, the following exclusions apply:
    - A bleeding disorder that is not under adequate control (including a plate count <50,000, international normalized ratio [INR] >1.5 or partial thromboplastin time [PTT] > upper limit of normal [ULN]).
    - Any contraindications to LP (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, or obesity to the extent that it makes LP technically difficult).

Study Treatment(s)

Study drug should be administered QD orally in the morning with or without food. Subjects will be instructed to take their other concomitant medications at the usual time.

Test drug: E2027

E2027 will be administered in size #2 hypromellose (HPMC) capsules containing 25 mg of E2027.

Subjects randomly assigned to E2027 dose will take 2 × E2027 25 mg capsules.

Comparator Drug: E2027-matched placebo capsules

Subjects randomly assigned to placebo will take 2 × E2027-matched placebo capsules QD.

Duration of Treatment

All subjects will receive 12 weeks of treatment.

Concomitant Drug/Therapy

Prohibited and Restricted Concomitant Medications:

Unless otherwise specified, the following medications are prohibited from a period of 14 days (or 5 half-lives, whichever is longer) before the Baseline Visit (Visit 2) until the Follow-Up Visit to avoid the risk of interaction with E2027. Subjects who start any of these medications during the study will be discontinued.

- Drugs known to be strong inhibitors of cytochrome P450 (CYP) 3A (CYP3A), which increase exposure of drugs that are CYP3A substrates by >5 fold, grapefruit, grapefruit juice, and grapefruit products.
- Drugs known to be moderate to strong inducers of CYP3A. Herbal preparations containing St. John's Wort is prohibited for 4 weeks before the Baseline Visit (Visit 2) until the Follow-Up Visit.
- Drugs known to cause prolongation of the QT interval, including but not limited to drugs that may cause cardiac arrhythmias. For drugs which may cause QTcF prolongation, subjects need not be excluded if at Screening the subjects are already on stable doses for at least 4 weeks and their mean QTcF on triplicate ECGs at Screening and Baseline Visit is not >450 ms (Exclusion Criterion 15).
- Drugs that are phosphodiesterase inhibitors (eg, theophylline, aminophylline, sildenafil, tadalafil, vardenafil, dipyridamole, roflumilast, apremilast, inamrinone, milrinone, and enoximone)

The following medications are prohibited to avoid the risk of interference with study assessments or procedures. Subjects who start these medications during the study will be discontinued unless otherwise specified.

- Anticholinergic drugs that have central nervous system (CNS) activity are prohibited from 4 weeks before Screening Visit until the Follow-Up Visit.
- Pimavanserin is prohibited for 12 weeks before Screening Visit until the Follow-Up Visit. (revised per Amendment 03)
- In subjects who participate in the CSF substudy only, anticoagulants (eg, heparin, heparin derivatives, non-heparin derivatives, warfarin, dabigatran) and dual antiplatelet therapy (eg, aspirin and clopidogrel together) are prohibited from Screening Visit until after the 2nd CSF collection at 9 weeks postrandomization. These subjects who start anticoagulants or dual antiplatelet therapy at any time before CSF collection at 9 weeks postrandomization will not participate in the CSF substudy.

The following restrictions apply to AChEIs (including donepezil, rivastigmine, galantamine) for treatment of DLB:

- If a subject is already receiving AChEI at Screening, they must be on a stable dose for at least 12 weeks before Screening and remain on the same dose during the study until the Follow-Up Visit.
- If a subject is not already receiving AChEI at Screening, then these should not have been used at least 12 weeks before Screening and AChEI should not be started during the study until the Follow-Up Visit.
- As far as it is feasible subjects who start AChEI or change their dose of AChEI during the study should undertake an Unscheduled Visit before making such changes in their AChEI medications to undertake efficacy assessments (MoCA, CIBIC-Plus, MMSE, SCOPA-Sleep, NPI, CFI, CGIC-DLB) (unless they have been conducted within past 4 weeks). This change in AChEI medication is considered a protocol deviation; the handling of efficacy data collected after the change of these medications in the efficacy analyses is described under Statistical Methods.

The following restrictions apply to memantine for treatment of DLB (revised per Amendment 03):

- If a subject is already receiving memantine at Screening, they must be on a stable dose for at least 12 weeks before Screening and remain on the same dose during the study until the Follow-Up Visit.
- If a subject is not already receiving memantine at Screening, then this should not have been used at least 12 weeks before Screening and memantine should not be started during the study until the Follow-Up Visit.
- As far as it is feasible subjects who start memantine or change their dose of memantine during the study should undertake an Unscheduled Visit before making such changes in their memantine to undertake efficacy assessments (MoCA, CIBIC-Plus, MMSE, SCOPA-Sleep, NPI, CFI, CGIC-DLB) (unless they have been conducted within past 4 weeks). This change in memantine is considered a protocol deviation; the handling of efficacy data collected after the change of these medications in the efficacy analyses is described under Statistical Methods.

The following restrictions apply to medications for Parkinson's disease or motor symptoms of DLB (except CNS-active anticholinergic drugs that are prohibited as above):

- If a subject is already on any of these medications at Screening, then they must be on a stable dose for at least 4 weeks before Screening and remain on the same dose during the study until the Follow-Up Visit.
- If a subject is not already on any of these medications at Screening, then these should not be started during the study until the Follow-Up Visit.
- Starting or changing the dose of these medications during the study is considered as a protocol deviation; the handling of efficacy data collected after the change of these medications in the efficacy analyses is described under Statistical Methods.

The following restrictions apply to medications for antipsychotic or neuroleptic drugs, Yi Gan San, hypnotics, anxiolytics or antidepressants:

- If a subject is already on any of these medications at Screening, then they must be on a stable dose for at least 4 weeks before Screening and remain on the same dose during the study until the Follow-Up Visit.
- If a subject is not already on any of these medications at Screening, then these should not be started during the study until the Follow-Up Visit.
- As far as it is feasible subjects who start or change their dose of these medications should undertake an Unscheduled Visit before making such changes in these medications to undertake

efficacy assessments (MoCA, CIBIC-Plus, MMSE, SCOPA-Sleep, NPI, CFI, CGIC-DLB) (unless they have been conducted within past 4 weeks). This change in such medications is a protocol deviation and the handling of efficacy data collected after the change of these medications in the efficacy analyses is described under Statistical Methods.

The following restrictions apply to other medications that the subject is taking at Screening or are started during the study:

- These medications may be permitted if they are not included in the prohibited or restricted medications list above, and are considered by the investigator and sponsor medical monitor not to compromise study assessments or subject safety.
- Permitted prior medications should be at a stable dose for at least 4 weeks before Screening and as far as possible remain on the same dose throughout the study.
- Subjects who change the dose of their permitted prior medications or who start permitted new medications during the study may continue in the study if the investigator and sponsor medical monitor consider that this will not compromise study assessments or subject safety.
- As needed (PRN) medications required for performing LP for CSF sampling are permitted in the CSF substudy.

Assessments

Efficacy Assessments

MoCA

This scale assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. It is reported to be useful to characterize global cognitive impairment in DLB. The total possible score is 30 points; a score of 26 or above is considered normal.

CIBIC-Plus

The CIBIC-Plus scale is designed to measure various domains that describe subject function: general, mental/cognitive state, behavior, and activities of daily living. It is a semi-structured global rating derived from a comprehensive interview with the subject and caregiver or informant by an independent rater who has no access to the source data or other psychometric test scores conducted postrandomization as part of the given protocol.

At Baseline Visit, the independent rater will use a related tool, the CIBIS-Plus. This scale, which assesses disease severity on a 7-point scale from 1 = normal to 7 = extremely ill, establishes a point of reference for subsequent interviews using the CIBIC-Plus. During study visits after 6 weeks and 12 weeks on study drug, the rater will administer the CIBIC-Plus separately to the subject and the caregiver or informant. At the end of each pair of interviews during each of these study visits, the rater alone will determine separately for each of the 4 domains whether the disease has improved, worsened, or remained unchanged since the evaluation at Baseline. The CIBIC-Plus scores are: 1 (marked improvement), 2 (moderate improvement), 3 (minimal improvement), 4 (no change), 5 (minimal worsening), 6 (moderate worsening) and 7 (marked worsening).

NPI

This scale assesses frequency and severity of 12 neuropsychiatric symptoms commonly described in dementia patients: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, nighttime behaviors and appetite/eating changes. The scale also assesses the degree of caregiver or informant distress engendered by each of the symptoms. It is rated from 0 to 144 with high scores meaning a

greater neuropsychiatric disturbance. A subscore covering the domains of delusions, hallucinations, apathy, and depression (NPI-4) will also be derived.

MMSE

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).

CFI

This scale assesses cognitive fluctuation with the same format as the NPI. It evaluates fluctuation in various domains including attention, ability to performance daily functions, orientation, verbal communication and behaviour. It is scored based on frequency and severity with a score range of 0 to 12. The scale also assesses the degree of caregiver or informant distress engendered by the symptoms.

SCOPA-Sleep

There are sections for night time and daytime sleep. There are 5 questions for night time sleep: (1) trouble falling asleep, (2) awakening during the night, (3) episodes lying awake too long at night, (4) early morning waking, and (5) patient's impression whether they had adequate duration of sleep at night. There are 6 questions for daytime sleep, (1) falling asleep unexpectedly during the day or evening, (2) falling asleep while sitting peacefully, (3) while watching television or reading, (4) while talking to someone, (5) trouble staying awake during the day or evening, and (6) experiencing falling asleep as a problem.

CGIC-DLB

The CGIC-DLB provides an overall clinician-determined summary measure of change from the subject's clinical status at Baseline Visit that takes into account all available information from the efficacy endpoints above (which include cognitive function, non-cognitive symptoms, behaviour and the impact of the symptoms on the patient's ability to function) and safety data.

PK Assessments

Blood samples will be collected for the determination of plasma E2027 concentrations for PK analysis. Two blood samples for PK will be drawn at Week 2: at predose (within 30 minutes before dosing) and 1 to 3 hours postdose. Three blood samples for PK will be drawn at Weeks 6 and 12: at predose (within 30 minutes before dosing), 1 to 3 hours, and 4 to 8 hours postdose. Additionally, 2 blood samples for PK will be drawn at Week 9: 1 at predose (30 minutes before dosing), and another at 1 to 4 hours postdose. At these visits, subjects or their caregivers or informants will be instructed not to take their study drug at home on the day the blood samples for PK are collected. Instead, subjects will take their study drug at the clinic after the predose blood draw; then a postdose blood draw will be performed. In addition, subjects or their caregivers or informant will be instructed to record the time of study drug administration for the 2 days before these visits when self-administered at home and this information will be collected and recorded on the electronic case report forms (eCRFs).

In subjects who participate in the CSF substudy, CSF specimens will be collected for the determination of CSF E2027 concentrations at Week 9. At this visit, a predose blood sample for PK will be taken first, followed by CSF sampling. Study drug will then be administered to the subjects.

PD Assessments

In subjects who participate in the CSF substudy, a CSF sample will be collected during the Screening Period (at least 7 days before the Baseline Visit) and after 9 weeks on study drug. Both samples should be collected at approximately the same time in the morning, either in the fasted state (preferred) or at least 2 hours after breakfast. The CSF sample during the Treatment Period should

be collected after the predose blood draw for PK analysis at the study visit after 9 weeks on study drug. The CSF samples will be assayed for cGMP and E2027. Other CSF PD biomarkers related to DLB or E2027 PD effects may also be assayed if appropriate.

PGx Assessments

Blood samples will be collected as specified in the Schedule of Procedures/Assessments where feasible and in accordance with local regulations. Participation in PGx assessments is voluntary and subjects must provide a separate informed consent before blood collection for PGx assessments.

The PGx blood samples may be used to genotype common and rare genetic variants. Data obtained from the PGx analysis will be used for research, to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The deoxyribonucleic acid (DNA) will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample may be stored for up to 15 years, based on country specific regulations to assist in any scientific research questions related to E2027 or DLB.

Safety Assessments

Safety will be assessed by monitoring and recording all AEs, monitoring of hematology, blood chemistry and urinalysis, measurement of vital signs (including orthostatic changes), ECGs, and the performance of physical examinations, C-SSRS and UPDRS-III. A safety brain MRI may also be performed at Unscheduled Visits if deemed appropriate by the investigator.

C-SSRS

An assessment of suicidality using the C-SSRS will be performed at Screening and Baseline Visits, every visit during the Treatment Period and at the Follow-Up Visit.

MDS UPDRS-III: Motor Examination

This scale evaluates extrapyramidal features in motor function in Parkinson's disease. It contains 33 items in 18 categories: (1) speech, (2) facial expression, (3) rigidity, (4) finger tapping, (5) hand movements, (6) supinational and pronation movements of hands, (7) toe tapping, (8) leg agility, (9) arising from chair, (10) gait, (11) freezing of gait, (12) postural stability, (13) posture, (14) body bradykinesia, (15) postural tremor of hands, (16) kinetic tremor of hands, (17) rest tremor amplitude and (18) constancy of rest tremor. Each item is scored 0 to 4, giving a total score range 0 to 132. As far as is practical, the motor assessments should be made with the subject in the "on" state at each visit and at the same time relative to the subject's last dose of Parkinson's disease medication (such as L-dopa). (revised per Amendment 01)

Other Assessments

DEMQOL and DEMQOL-Proxy

The DEMQOL and DEMQOL-Proxy are appropriate for use in subjects with mild-moderate dementia (MMSE ≥10). The DEMQOL is a 28-item scale and DEMQOL-Proxy is a 31-item scale. Both are interview administered. Should the subject progress to severe dementia during the course of the study, only the DEMQOL-Proxy should be administered. There are 5 domains: daily activities, health and well-being, cognitive functioning, social relationships and self-concept. All items are given a score from 1 to 4 and summed to produce domain scores. A general quality of life item is unscored.

EQ-5D

The EQ-5D is a widely used general health state and health utility scale to assess the impact of any health intervention on the patient's general quality of life. The health utility values are utilized as weights to life expectancy estimates and ultimately are used in a metric known as an incremental

cost effectiveness ratio (ICERs). ICERs are used by health authorities to make key decisions that ultimately impact the relative funding of health interventions across multiple therapeutic areas based on their relative cost-effectiveness. Thus, the EQ-5D is not specifically developed for any particular disease to allow this cross-therapeutic comparison. The scale consists of 5 specific questions (regarding mobility [walking], self-care [washing and dressing], usual activities, pain/discomfort, and anxiety/depression) and 1 overall health rating. The EQ-5D is selected in this study due to its brevity and content. The EQ-5D-5L (5 levels of responses to each of the 5 questions) will be utilized in this study as it allows for a more granular assessment of the impact of intervention. The proxy EQ-5D version is available as EQ-5D-5L (5 levels of responses to each of the 5 questions) and will be utilized to assess the caregiver's or informant's perspective of the subject's health. The proxy EQ-5D-5L is available in 2 versions: Proxy version 1 where the caregiver or informant (the proxy) is asked to rate the subject's health-related quality of life in their (the proxy's) opinion and Proxy version 2 where the caregiver or informant (the proxy) is asked to rate how he/she (the proxy) thinks the subject would rate his/her own health-related quality of life, if the subject were able to communicate it. Only Proxy version 1 will be utilized in this particular study.

Bioanalytical Methods

Plasma and CSF E2027 concentrations and those of its metabolites (if appropriate) will be measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay methods. CSF cGMP concentrations will be measured using a validated LC-MS/MS assay method.

Statistical Methods

Study Endpoints

Primary Endpoints

- Change from baseline in the MoCA total score at 12 weeks of treatment
- CIBIC-Plus scale at 12 weeks of treatment

Secondary Endpoints
(Order revised per Amendment 05)

- CGIC-DLB scale at 12 weeks of treatment
- Change from baseline at 12 weeks of treatment in the following endpoints:
  - CFI score
  - MMSE total score
  - NPI total score, subscores and caregiver or informant distress score
- Safety and tolerability of E2027 as measured by (revised per Amendment 02):
  - Incidence of adverse events including severe AEs, serious AEs, AEs resulting in discontinuation
  - Incidence of orthostatic hypotension and orthostatic tachycardia
  - Incidence of markedly abnormal laboratory values and shifts from baseline of laboratory values
  - Incidence of abnormal ECG parameters and abnormal ECG findings
  - Incidence of suicidality based on C-SSRS
  - Changes from baseline in the total score of Unified Parkinson's Disease Rating Scale Part III: Motor Examination (UPDRS-III).

Exploratory Endpoints

- Change from baseline at 12 weeks of treatment in the following endpoints:

- SCOPA-Sleep total score and subscores

- Change from baseline at 12 weeks of treatment in the following endpoints:
  - Each of the 5 domain scores of the DEMQOL and DEMQOL-Proxy
  - EQ-5D utility score and EQ-5D health status rating
- Percentage change from baseline in CSF cGMP concentration after 9 weeks of treatment

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 postrandomization 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 postrandomization coprimary efficacy measurement
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol. It may include subjects who complete certain prespecified minimal exposure to the treatment and have no major protocol violations such as wrong diagnosis, error in treatment assignment, use of prohibited medication and poor compliance. The precise reasons for excluding subjects from the PPS will be fully defined and documented before database lock.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable plasma E2027 concentration with a documented dosing history
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter
- The PK/PD Analysis Set is a group of subjects with at least 1 quantifiable plasma E2027 concentration, except for placebo subjects, and at least 1 PD measurement with a documented dosing history.

Efficacy Analyses

The significance level for all efficacy endpoint analyses is 0.05 (2-sided), unless otherwise stated, with no adjustments for multiplicity. The efficacy analyses will be performed on the FAS except per protocol analysis will be performed on the PPS.

Definitions of Baseline

Baseline for the primary and secondary efficacy endpoints is defined as the last pretreatment assessment. An additional baseline, based on the mean of all prerandomization values at the Screening and Baseline assessment, will be explored due to assess potential prerandomization variability.

Analysis for the Primary Efficacy Endpoints

E2027 is planned for use as a symptomatic treatment in subjects with DLB. The treatment effect of E2027 may be confounded by the use of rescue medications during the study. For the purposes of statistical analysis, rescue medications are defined as medications for treatment of symptoms of DLB that are prohibited or restricted (as specified in Concomitant Drug/Therapy section above) and they are not used in accordance with the rules in Concomitant Drug/Therapy section. This confounding may mask the true treatment effect of E2027 in treating subjects with DLB. The treatment effect of interest will be the efficacy as measured by coprimary endpoints that would be observed at 12 weeks without initiation or dose change of any prohibited or restricted medications as mentioned above regardless of whether or when the assigned treatment was discontinued due to adverse event, lack of

efficacy or any other events related to treatment or study outcome. The target population is DLB subjects defined by inclusion/exclusion criteria.

There are 2 coprimary efficacy endpoints, change from baseline in the MoCA total score at 12 weeks and CIBIC-Plus scale at 12 weeks. Overall, there are 2 null hypotheses (H_0) to be tested in the primary analysis:

- H_{01}: There is no difference in the mean change from baseline in the MoCA total score at 12 weeks between E2027 and placebo.
- H_{02}: the proportional odds ratio based on CIBIC-Plus scale at 12 weeks between E2027 and placebo is equal to 1.

The corresponding 2 alternative hypotheses are that there is a difference in the mean change from baseline in MoCA total score at 12 weeks in this coprimary endpoint between E2027 and placebo, and the proportional odds ratio based on CIBIC-Plus scale at 12 weeks between E2027 and placebo is not equal to 1. The study will be considered positive if statistically significant improvement (at level of 0.05 (2-sided) or 0.025 (1-sided)) is observed in both coprimary endpoints in E2027.

The change from baseline of MoCA total score for E2027 compared to placebo will be analysed using the approach proposed by Mehrotra, et al. (2017) with slight modification based on reasons for missing data. The following is a list of reasons for missing data and their missing mechanisms:

- Data not observed because of dropouts due to AEs, lack of efficacy or any other intercurrent events related to treatment or study outcome will be considered as missing not at random (MNAR)
- The effect had rescue medication not been made available to subjects prior to week 12 is not observable for subjects who initiated prohibited or restricted rescue medication. For these subjects, the data collected after initiation of prohibited rescue medication are assumed to contain no treatment effect in the E2027 treatment group. Technically, response data collected after initiation of prohibited rescue medication will be treated as MNAR such that response data as MNAR in the E2027 treatment group would be imputed by the mean response in the placebo treatment group as described by the imputation method below.
- Data not observed because of dropouts due to intercurrent events definitely not related to treatment or outcome (eg, withdraw consent due to logistical problems) will be considered as missing at random (MAR). All events will be classified unambiguously in the statistical analysis plan.

The mean of missing endpoint values in the E2027 treatment group considered as MAR will be imputed using the mean of missing endpoint values of completers in the E2027 treatment group and the mean of missing endpoint values in E2027 treatment group considered as MNAR will be imputed by the mean of the overall endpoint distribution under placebo based on the above missing reasons and the corresponding missing mechanisms. The mean of the overall endpoint distribution under placebo will be obtained using mixed effects model of repeated measures (MMRM) within placebo group assuming MAR. Test statistics and the p-value will be obtained as described by Mehrotra, et al. (2017).

The sensitivity analysis for MoCA will be a tipping point analysis based on control-based mean imputation proposed by Mehrotra, et al. (2017) in the same article, which is an increasingly more conservative means such that the *P*-value is equal to the prespecified alpha (0.025 [1-sided]). Drug benefit is interpreted as convincing if the tipping point is worse than the mean placebo dropouts. Additional sensitivity analysis for different classification of missing mechanism (ie, all missing data in the E2027 treatment group will be considered as MNAR regardless of reason of dropouts), will be provided.

In order to generate inputs for proposed primary and sensitivity analyses, a MMRM will be used in separate MMRM analyses for each treatment group for all randomized subjects as well as completers assuming MAR for both treatment groups. The model will be adjusted for baseline MoCA, visit (Week 6 and Week 12), randomization stratification variable (receiving AChEI or not, geographical region [North America, Europe, Japan]), and baseline MoCA × visit as fixed effects. An unstructured covariance matrix will be used to model the covariance of within subject effect. The values of baseline MoCA will be adjusted using the overall baseline mean of all study subjects in computing least square (LS)-means.

The primary analysis of the CIBIC-Plus scale at 12 weeks will be based on control-based pattern imputation at subject level (Yuan, 2014). The CIBIC-Plus scale at 12 weeks will be imputed as an ordinal response variable. The same missing reasons and corresponding missing mechanism as in the analysis of change from baseline in MoCA total score will be used in this analysis. Only the missing ordinal responses in E2027 treatment group considered as MNAR will be imputed by ordinal responses observed in the placebo group using a pattern-mixture model approach under MNAR assumption. Other missing ordinal responses will be imputed assuming MAR. The CIBIC-Plus scale at 12 weeks (observed or imputed) will be analysed using the proportional odds model, a special case of generalized linear mixed models (GLMM), in multiply imputed data sets. The results obtained from all multiply imputed data sets will be combined for overall inference using Rubin's rules. The GLMM model will include treatment, randomization stratification variables (receiving AChEI or not, geographical region [North America, Europe, Japan]) as fixed effects. The model will be fitted using GLMM with a multinomial distribution and a cumulative logit link function. The proportional odds ratio estimate between E2027 and placebo, the corresponding 95% CI and *P*-values will be presented.

The sensitivity analysis for the CIBIC-Plus scale will be a tipping point analysis based on multiple imputation at subject level using the pattern mixture model approach (Yuan, 2014), which is based on an increasingly more conservative shift parameter (based on cumulative logit function values for the CIBIC-Plus scale) such that the *P*-value is equal to the prespecified alpha (0.05 [2-sided]). Additional sensitivity analysis for different classification of missing mechanism (ie, all missing data will be considered as MNAR regardless of reason of dropouts), will be provided.

If the proportional odds assumption is contradicted by the observed data in either the entire population or any stratum, the GLMM method will be replaced by the nonparametric van Elteren test in both primary analysis and sensitivity analysis. The CIBIC-Plus scale at 12 weeks will be analysed using van Elteren test adjusting 2 randomization stratification variables (on stabilized AChEI dose or not; geographical region [North America, Europe, Japan]). The H_0 corresponding to the van Elteren test is that there is no difference in the location of distribution of the CIBIC-Plus scale at 12 weeks between E2027 and placebo. The corresponding alternative hypothesis is that there is a difference in the location of distribution of the CIBIC-Plus scale at 12 weeks between E2027 and placebo.

The potential effect of baseline MMSE on the primary result will be evaluated as an additional covariate in the primary model as appropriate. Subgroup (eg, region, age group, baseline AChEI status, baseline MMSE group, and baseline memantine status) analyses will be performed as appropriate. (revised per Amendment 03)

Analyses for the Secondary Efficacy Endpoints

The CGIC-DLB scale will be analysed as ordinal response data in a manner similar to the primary analysis of coprimary endpoint based on CIBIC-Plus. Other secondary endpoints are continuous

variables and will be analyzed in a manner similar to the primary analysis of coprimary endpoint based on MoCA.

Analyses for the Exploratory Efficacy Endpoints

The sleep endpoint (SCOPA-Sleep total score and subscores) will be analyzed in a manner similar to the primary analysis of the coprimary endpoint based on MoCA.

If data permit, the relationship between E2027 PD effects on CSF cGMP (and other biomarkers) and various efficacy endpoints will be explored using correlation analysis and linear models will be fitted to further characterize the relationship between the changes in efficacy endpoints and the changes in E2027 PD variables as appropriate.

PK, PD, and PGx Analyses

PK Analyses

The PK Analysis Set will be used for plasma E2027 concentration listings and for summaries of CSF E2027 concentrations by dose and day.

A population PK approach will be used to characterize plasma E2027 PK. For this approach, PK data from this study will be pooled with existing data from Phase 1 studies. The effect of covariates on plasma E2027 PK, such as baseline characteristics/demographics, will be evaluated where feasible. Derived plasma E2027 exposure parameters, such as steady state area under the concentration time curve (AUC_{ss}) or average steady state concentration ($C_{ss,av}$), will be calculated from the final PK model using the individual posterior estimates of the PK parameters and dosing history.

PD Analyses

The PD Analysis Set will be used for the summaries and analyses of CSF PD biomarkers. The percentage change from baseline in CSF cGMP and any other PD biomarkers after at least 9 weeks of treatment with study drug postrandomization will be analyzed and presented graphically.

PD/PK Analyses

Data combining Phase 1 studies, permitting a population PK/PD approach, will be used to characterize the relationship between plasma and/or CSF E2027 exposures and CSF PD biomarker levels. For this approach, data from this study will be pooled with relevant data from Phase 1 studies. The relationship between plasma and CSF E2027 exposure and the change from baseline of various efficacy endpoints will be explored graphically, as will the relationship between changes in CSF PD biomarkers and the change from baseline of various efficacy endpoints. Any emergent relationships will be explored through population PK/PD modeling.

PGx Analyses

Pharmacogenomic analyses may be performed and reported separately. Details of these analyses may be described in a separate analysis plan.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality (C-SSRS), UPDRS-III, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements (including orthostatic changes) will be summarized by treatment group.

Other Analyses

The quality of life endpoints (DEMQOL and DEMQOL-Proxy domain scores, and the EQ-5D and EQ-5D Proxy scores) after 12 weeks of treatment and the percentage change from baseline in CSF cGMP concentrations after 9 weeks of treatment will be analysed using ANCOVA or rank-based ANCOVA as appropriate. The ANCOVA model will include baseline as a covariate, with treatment group and randomization stratification variables as factors.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. (revised per Amendment 03)

Sample Size Rationale

The MoCA scale was assessed in DLB subjects and reported by Biundo et al. (2016). The observed mean change from baseline in the MoCA total score at 1 year in this report is -1.04 points and the corresponding standard deviation (SD) is 1.32 points. An estimation of the mean change from baseline in the MoCA total score at 3 months is approximately -0.26 points using linear interpolation. It is assumed that E2027 would improve the MoCA total score as compared with baseline and achieve a mean treatment difference of approximately 0.6 points between E2027 and placebo at 12 weeks. The SD of change from baseline in the MoCA total score at 3 months is expected to be smaller than that at 1 year. A conservative estimate of the SD of change from baseline in the MoCA total score is 1.3 points at 12 weeks.

In a 12-week donepezil monotherapy study in subjects with DLB (E2020-J081-431), the estimated proportional odds ratio based on the CIBIC-Plus scale for donepezil 10 mg relative to placebo was 6.14. It is assumed that E2027 would achieve a proportional odds ratio of 2.607 relative to placebo (ie, 42% of the effect size observed in the above donepezil study).

With 80 subjects completing per arm (for 91 randomized subjects per arm, assuming a 12% dropout rate), this study will have approximately 80% power to detect the above effect sizes (ie, mean treatment difference of approximately 0.6 points based MoCA total score and proportional odds ratio of 2.607 based on CIBIC-Plus scale for E2027 relative to placebo) in both coprimary endpoints simultaneously. Therefore, the total sample size of 182 randomized subjects is planned, assuming a 12% dropout rate.

Participation in the CSF substudy is voluntary. It is estimated that approximately 30% of subjects will participate in the CSF substudy. If the dropout rate in the CSF substudy is 12%, 20%, or 50%, then the number of subjects having final CSF assessment would be approximately 48, 44, or 27, respectively. The estimated standard deviation of percent change from baseline of cGMP concentrations after 9 weeks of treatment from pooled subjects in the CSF substudy is approximately 130%. The width of the 95% CI of the mean difference of percent change from baseline of cGMP concentrations after 9 weeks of treatment between E2027 and placebo for the 3 different sample sizes above would be approximately 74%, 77%, or 96%, respectively. Since mean percent change from baseline of cGMP concentrations after 9 weeks of treatment in the E2027 and placebo groups are expected to be approximately 200% and 5%, respectively, the sample size of the CSF substudy would be adequate to detect the mean difference of percent change from baseline of cGMP concentrations after 9 weeks of treatment between E2027 and placebo groups.

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
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADME	absorption, distribution, metabolism, and excretion
ALT	alanine aminotransferase (serum glutamic pyruvic transaminase)
A_{max}	maximum change (%) of CSF cGMP concentration compared to baseline at a single time point within 30 hours postdose
$A_{min,ss}$	minimum change (%) of CSF cGMP concentration at steady state compared to baseline
ANCOVA	analysis of covariance
AST	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUAC	area under the CSF cGMP concentration- time curve
AUC	area under the concentration-time curve
$AUC_{(0\text{-}24h)}$	area under the concentration-time curve from zero time to 24 hours postdose
$AUC_{(0\text{-}96h)}$	area under the concentration-time curve from zero time to 96 hours postdose
$AUC_{(0\text{-}144h)}$	area under the concentration-time curve from zero time to 144 hours postdose
AUC_{ss}	steady state area under the concentration time curve
$AUC_{(0\text{-}inf)}$	area under the concentration-time curve from zero time extrapolated to infinite time
$AUC_{(0\text{-}\tau)}$	area under the concentration-time curve from zero time to time of last quantifiable concentration
BP	blood pressure
cAMP	cyclic adenosine monophosphate
$C_{ss,av}$	average steady state concentration
CI	confidence interval
CIBIC-Plus	Clinician's Interview Based Impression of Change Plus Caregiver Input
CGIC-DLB	Clinician Global Impression of Change in Dementia with Lewy Bodies
cGMP	cyclic guanosine monophosphate
CFI	Cognitive Fluctuation Inventory
CL/F	apparent total clearance following oral administration
C_{max}	maximum observed concentration
$C_{max,SS}$	maximum observed concentration at steady state
C_{min}	minimum observed concentration
CNGCs	cyclic nucleotide-gated cation channels
CNS	central nervous system

Abbreviation	Term
CRAs	Clinical research associates
eCRF	electronic case report form
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
CYP3A	cytochrome P450 3A
DAT	dopamine transporter
DBP	diastolic blood pressure
DEMQOL	Dementia Quality of Life Measure
DEMQOL-Proxy	Dementia Quality of Life Measure by Proxy
DLB	dementia with Lewy bodies
DNA	deoxyribonucleic acid
DSMB	data safety monitoring board
DSM-V	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
ECG	Electrocardiogram(s)
ECL	enterochromaffin-like
e-COA	Electronic Clinical Outcome Assessment
ED	early discontinuation
EQ-5D	EuroQol- 5 Dimension questionnaire
EQ-5D Proxy	EuroQol- 5 Dimensions questionnaire by Proxy Version 1
ER	extended release
FAS	Full Analysis Set
GC	guanylyl cyclase
GDS	Geriatric Depression Scale
GGT	γ-glutamyl transpeptidase
GLMM	generalized linear mixed models
GM	geometric mean
GTP	guanosine triphosphate
H_{01}, H_{02}	null hypothesis 1 to 2, respectively
hCG	human chorionic gonadotropin
HPMC	hypromellose
HR	heart rate
HYS	Hoehn and Yahr Scale
IAG	Imaging Charter and Imaging Acquisition Guidelines
IC_{50}	50% inhibitory concentration

Abbreviation	Term
ICER	incremental cost effectiveness ratio
ICF	informed consent form
IEC	Independent Ethics Committee
INR	international normalized ratio
IUPAC	International Union of Pure and Applied Chemistry
IUS	intrauterine hormone-releasing system
IxRS	interactive voice and web response system
LBD	Lewy body dementias
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LLN	lower limit of normal
LP	lumbar puncture
LS	least square
LTP	long-term potentiation
MAD	multiple-ascending dose study
MAR	missing at random
MDS	Movement Disorders Society
MIBG	^{123}I-meta-iodobenzylguanidine
MMRM	mixed effects model of repeated measures
MMSE	Mini-Mental State Examination
MNAR	Missing not at random
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NMDA	N-methyl-D-aspartate
NOAEL	no observed adverse effect level
NPI	Neuropsychiatric Inventory
NPI-4	NPI subscore covering 4 domains: delusions, hallucinations, apathy, and depression
N/A	not applicable
NOS	nitric oxide synthase
PD	Pharmacodynamic(s)
PDD	Parkinson disease dementia
PDE	Phosphodiesterase(s)
PDE9A	phosphodiesterase 9
PET	positron emission tomography

Abbreviation	Term
PGx	pharmacogenomic
PK	Pharmacokinetic(s)
PKG	cGMP-dependent protein kinase
POC	proof of concept
PPK	population pharmacokinetics
PPS	Per Protocol Analysis Set
PRN	as needed (pro re nata)
PSG	polysomnography
PTT	partial thromboplastin time
QD	once daily
QTcF	corrected QT interval calculated using Fridericia's formula
RBC	red blood cell
REM	rapid eye movement
SAD	single ascending dose
SBP	systolic blood pressure
SCOPA-Sleep	Scales for Outcome in Parkinson's disease-Sleep
SD	standard deviation
SFQ	Short Fluctuation Questionnaire
SOP	standard operating procedure
SPECT	single-photon emission computed tomography
$t_{½}$	terminal elimination phase half-life
T3	triiodothyronine
T4	thyroxine
TEAEs	treatment-emergent adverse events
t_{max}	time to reach maximum peak concentration following drug administration
TFT	thyroid function tests
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UPDRS-III	Unified Parkinson's Disease Rating Scale Part III: Motor Examination
WBC	white blood cell
β-hCG	beta-human chorionic gonadotropin
$\Delta AUAC_{(0\text{-}30h)}$	AUAC averaged over 30 hours postdose relative to baseline AUAC averaged over 3 hours predose for CSF cGMP, ie, $(AUAC_{(0–30h)}/30 - AUAC_{(-3–0h)}/3)/(AUAC_{(-3–0h)}/3)$
ΔΔQTcF	placebo-corrected change-from-baseline in corrected QT interval calculated using Fridericia's formula

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 ICH E6 (Good Clinical Practice), 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[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 investigator(s) 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.

Where appropriate, at the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

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 (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
- A waiver from the IRB(s)/IEC(s) will be obtained before study initiation for non-US studies conducted under an Investigational New Drug application (IND).
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU 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 must explain to each subject or caregiver (or informant) in accordance with applicable professional standards and local laws/regulations 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 or the subject's legally acceptable representative 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 a legally acceptable representative 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 or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative 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 before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The subject's capacity to consent must be assessed at periodic intervals during the course of the subject's involvement in the study, including whenever any concern is expressed about the subject's continued capacity to consent (eg, by the study partner or a subject's family member). The method and frequency of the assessment of capacity to consent must be performed in accordance with applicable professional standards and local laws/regulations. During the course of the study, should a subject, in the investigator's opinion, decline to the point of lacking capacity to consent, the investigator should obtain the assent of the subject and the consent of their designated representative per the applicable local laws/regulations and IRB/IEC standards in order for the subject to continue in the study. In countries where local laws/regulations do not permit subjects lacking capacity to consent to participate in this study, then subjects who have declined to the point of lacking capacity to consent during the study will be discontinued. (revised per Amendment 02)

The identified caregiver or informant should also consent to supporting the subject's participation in the study before any study-specific procedures are performed and will be provided with a written ICF for his or her participation in the study. The subject and caregiver or informant do not have to sign their ICF on the same day.

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 identified caregiver or informant will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or their designated representative per the applicable local laws/regulations and IRB/IEC standards 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.

Subjects who agree to take part in the cerebrospinal fluid (CSF) substudy will be asked to provide separate written consent for these procedures. Subjects who agree to take part in pharmacogenomics (PGx) assessment will also be asked to provide separate written consent for this procedure.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 70 investigational sites in North America, Europe, and Japan. (revised per Amendment 03)

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 site files that are provided to each site.

7 INTRODUCTION

7.1 Indication

Lewy body dementias (LBD) are the second most common cause of dementia in subjects over 65 years of age. It comprises dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), which are considered to be different ends of the same spectrum. Both DLB and PDD share a common underlying pathology which involves deposition of cortical and subcortical Lewy bodies within neurons (comprising aggregates of alpha synuclein). Idiopathic Parkinson's disease is a progressive neurodegenerative disorder characterized by tremor, rigidity, bradykinesia, and postural instability, with onset typically in middle to late life. It is thought that up to 80% of patients with Parkinson's disease develop dementia some years after the onset of the motor features and they are classified as having PDD. In DLB, subjects develop dementia prior to or within 12 months (McKeith, et al., 2017) after the onset of the characteristic motor symptoms associated with Parkinson's disease (Walker, et al., 2015).

LBD (in the form of both DLB and PDD) involve similar profiles of cognitive dysfunction affecting attention, executive function, visuospatial domains and memory (Aarsland, et al., 2003, Walker, et al., 2015, Biundo, et al., 2016). Often, more than 1 aspect of cognition is impaired, interfering with the patient's daily, occupational or social functioning. While generally progressive, LBD are characterized by fluctuations in cognition and levels of consciousness, visual hallucinations, delusions, depression, anxiety, or other behavioral disturbances. Patients may also have autonomic impairment that may include urinary dysfunction and orthostatic hypotension, with susceptibility to falls early in the disease course.

Although both DLB and PDD are considered to be part of the same spectrum of LBD, there are some clinical differences. DLB subjects develop dementia early in the course of their disease (McKeith, et al., 2017) compared to subjects with PDD. Patients with PDD have motor symptoms for some years with a higher proportion taking medications for Parkinsonian motor symptoms (Noe, et al., 2004). Neuropsychiatric features (such as visual hallucinations) and cognitive fluctuations are more prominent in DLB than in PDD. In DLB ~30% of subjects have concurrent amyloid pathology in the brain similar to that in Alzheimer's disease (AD), whereas brain amyloid levels are lower in PDD compared to DLB (Donaghy, et al., 2015).

7.1.1 Current Therapeutic Options

There are no therapies currently available that alter the underlying neurodegenerative process of LBD. A number of symptomatic therapies can improve patient quality of life, primarily through management of motor symptoms such as bradykinesia, rigidity and gait disturbance. Levodopa remains the most effective medication available for treating the motor features of Parkinson's disease that occur in LBD. Current therapy for cognitive deficits associated with

LBD is largely based on the use of acetylcholinesterase inhibitors (AChEIs), such as rivastigmine and donepezil. Rivastigmine is approved in multiple countries for symptomatic treatment of cognitive deficits in PDD and donepezil is approved in several Asian countries including Japan and the Philippines for symptomatic treatment of DLB. Memantine is also used in the treatment of DLB but its efficacy is small (Aarsland, et al., 2009). (revised per Amendment 03) With regard to neuropsychiatric symptoms, pimavanserin is approved for these symptoms in Parkinson's disease. AChEIs and antipsychotics such as risperidone, quetiapine, and olanzapine are also commonly used in clinical neurology practice for this purpose. However, the efficacy of AChEI and antipsychotic drugs on cognitive symptoms and neuropsychiatric symptoms is modest. In addition, there are concerns about worsening of parkinsonism by both AChEI and antipsychotics as well as special concerns about hypersensitivity to antipsychotics. Therefore, there is need for further treatment benefit.

7.1.1.1 Therapeutic Pathway

E2027 is a novel highly selective and potent inhibitor of PDE9. PDE9 is primarily responsible for breakdown of cyclic guanosine monophosphate (cGMP) within the brain, and the decreased levels of this secondary messenger have been associated with lower cognitive function in subjects with AD. By inhibiting PDE9, and therefore reducing breakdown of cGMP, E2027 aims to restore cGMP levels within the brain, and therefore palliate the symptoms in LBD.

7.1.1.2 Clinical Experience With E2027

As of the cut-off date of 30 Oct 2017, E2027 has been evaluated in 2 completed studies (E2027-A001-001 [Study 001] and E2027-A001-003 [Study 003]) and 1 ongoing study (E2027-A001-002 [Study 002]). Overall, 186 subjects have received single or multiple doses of E2027 or placebo in the completed and ongoing studies as of the cut-off date. Of these, final or quality controlled data are available for 112 subjects administered single E2027 doses from 10 to 1200 mg and for 36 subjects administered multiple doses of E2027 from 25 to 400 mg for 2 weeks.

Detailed description of clinical experience with E2027 is provided in the E2027 Global Investigator's Brochure.

7.1.1.2.1 PHARMACOKINETICS AND PHARMACODYNAMICS

In Study 001, healthy subjects (aged 18 to 50 years), E2027 was rapidly absorbed after single doses of 10 to 1200 mg, with most subjects having quantifiable plasma E2027 concentrations within 0.5 hour post-dose. Across all doses, the median t_{max} ranged from 2 to 4 hours post-dose and E2027 showed biphasic disposition after t_{max}. During the initial phase, plasma E2027 concentrations declined until approximately 12 hours post-dose and then remained relatively stable through 24 hours post-dose. At all doses there were subjects who showed multiple secondary peaks during the first 24 hours post-dose. It was possible that the secondary peaks were due to the absorption of E2027 occurring in multiple stages. From 24 hours post-dose onwards, E2027 showed first order kinetics during the terminal elimination phase. Mean half-life was ~30 hours across doses (10 to 1200 mg), with no trend of increasing half-life values with increasing dose. Overall the geometric mean (GM) C_{max} and $AUC_{(0\text{-inf})}$ values

increased sub-proportionally with increasing doses from 10 to 1200 mg. Geometric mean CL/F values showed a trend to increase with increasing dose. Over the E2027 dose range of 10 to 1200 mg, less than 1% of unchanged E2027 was eliminated in urine, suggesting that renal excretion is not an important elimination pathway for E2027 in humans.

Administration of a single dose of E2027 100 mg after consuming a standardized high-fat and high-calorie meal resulted in a 44.4% increase in the GM C_{max} and a 19.2% increase in the GM $AUC_{(0\text{-inf})}$. This difference is not considered clinically significant and E2027 may be administered with or without food.

In healthy elderly subjects administered E2027 100 mg, the GM LS C_{max} was approximately 45.5% higher and GM LS $AUC_{(0\text{-inf})}$ was approximately 41.5% higher than in younger healthy adult subjects. The mean $t_{½}$ in healthy elderly subjects was approximately 10 hours longer than in younger healthy adult subjects.

Preliminary PK data in Study 002, healthy subjects (aged 50 to 85) who were treated with E2027 at 25 mg to 400 mg QD for 14 days showed that after the first dose on Day 1, the PK profile was similar to that seen in the first time in human single ascending dose study. Thereafter, steady state was reached by Day 12. After the final dose on Day 14, the steady state PK profile was similar to that of Day 1. E2027 was rapidly absorbed with median t_{max} ranging from 1.5 to 3.0 hours postdose. Thereafter, plasma E2027 concentrations declined until approximately 12 hours postdose and then remained relatively stable to 24 hours postdose of Day 14. At all doses there were subjects who showed secondary peaks at approximately 24 hours postdose of Day 14. From 24 hours postdose onwards, E2027 showed first order kinetics during the terminal elimination phase. Mean half-life after Day 14 was similar across doses, at ~40 hours, with no trend of increasing half-life with increasing dose. The accumulation ratios of C_{max} and $AUC_{(0\text{-}24h)}$ were generally consistent with the estimate from single-dose PK (~2.95-fold accumulation). Overall the mean C_{max} and AUC at steady state increased subproportionally with increasing doses from 25 to 400 mg, consistent with single dose PK characteristics. For a 16-fold increase in dose from 25 to 400 mg, $C_{max,ss}$ increased by 8.4 fold and $AUC_{(0\text{-}\tau)}$ increased by 7.7 fold. The ratio of CSF:plasma concentrations of E2027 at steady state was ~3.5%.

Healthy Japanese subjects administered E2027 400 mg QD for 14 days showed comparable $C_{max,ss}$ and $AUC_{(0\text{-}\tau)}$ as non-Japanese subjects. Their half-life and accumulation ratios at steady state were comparable to non-Japanese subjects administered E2027 400 mg QD. Therefore, no dose adjustment compared to non-Japanese subjects is required when E2027 is administered to Japanese subjects.

In the presence of diltiazem (as a strong CYP3A inhibitor and P-gp inhibitor) administered at steady state, the C_{max} of a single dose of E2027 100 mg increased by 14% and $AUC_{(0\text{-inf})}$ increased by 51%. Thus, diltiazem had a mild inhibitory interaction with E2027 metabolism. Therefore, it is anticipated that mild to moderate inhibitors of CYP3A and P-gp inhibitors will have minimal effects on E2027 PK and are not likely to be clinically significant. Therefore, no dose adjustments are required when E2027 is administered with concomitant medications that are mild-to-moderate CYP3A inhibitors or P-gp inhibitors.

In Study 002, subjects administered 5 to 400 mg QD for 14 days underwent CSF collection at baseline and at steady state on Day 13 near the end of their treatment to evaluate CSF PK and PD effects (CSF cGMP elevation). In addition, there were subjects administered E2027 50 mg QD for 6 weeks who underwent CSF collection at baseline and at steady state on Day 13 and Day 41 to evaluate CSF PK and PD effects (CSF cGMP elevation).

At all E2027 doses (5 mg QD to 400 mg QD for 14 days), there was an increase in CSF cGMP concentrations (PD effect) from baseline as shown in Table 1. The distribution of the PD effects in CSF overlapped across various doses. Although the mean PD effects in CSF were greater at E2027 100 mg QD × 14 days than 50 mg QD × 14 days, this could in part be due to a potential outlier in the 100 mg cohort. In general, across all E2027 doses studied (25 – 400 mg QD × 14 days) there was no dose related increase in CSF cGMP concentrations.

Table 1 Mean PK Parameters and Mean Increase in CSF cGMP From Baseline at Steady State In Study E2027-A001-002

Dose	$C_{max,ss}$ (ng/mL)	$AUC_{(0-\tau)}$ (ng·h/mL)	CSF cGMP↑ From Baseline Predose at Steady State $A_{min,ss}$ (%)
5 mg QD	61.7	865	34
10 mg QD	137	1940	94
25 mg QD	336	5210	170
50 mg QD	788	11800	191
100 mg QD	1020	16800	260
200 mg QD	1780	24300	201
400 mg QD	2395	43638	199

$AUC_{(0-\tau)}$ = area under the concentration-time curve from zero time to time of last quantifiable concentration, $A_{min,ss}$ = minimum change (%) of CSF cGMP concentration at steady state compared to baseline, cGMP = cyclic guanosine monophosphate, $C_{max,ss}$ = maximum observed concentration at steady state, CSF = cerebrospinal fluid, QD = once daily.

In subjects treated with 50 mg QD for 6 weeks it was found that the CSF cGMP increased from baseline by 229% on Day 13 and by 222% on Day 41. Thus the CSF PD effects were sustained over a treatment period of up to 6 weeks in subjects administered E2027 50 mg QD.

7.1.1.2.2 SAFETY AND TOLERABILITY

Single Dose Study 001

E2027 was well tolerated in healthy adult subjects when administered as single oral doses across the dose range of 10 to 1200 mg. The maximum tolerated dose (MTD) was not reached within the 120-fold range of increasing doses. There were no dose-related trends in the incidence of various treatment-emergent adverse events (TEAEs). The most common TEAEs (reported in more than 1 subject) in Study 001 occurring in subjects treated with E2027 were headache (11.6%), postural orthostatic tachycardia (5.6%), dizziness (5.6%), insomnia (5.6%),

increased in orthostatic HR response (3.7%) and paresthesia (3.7%). Headache appeared to have a higher incidence in subjects on placebo. Most TEAEs were of mild severity.

There were no clinically significant changes in hematology, biochemistry and urinalysis values or in BP, HR, respiratory rate, and body temperature associated with single doses of E2027 at 10 mg to 1200 mg. There were no dose-related trends to indicate that E2027 was associated with orthostatic tachycardia or orthostatic hypotension. There were no effects of E2027 on ECG morphology, HR, PR interval and QRS interval. The exposure-response relationship of the ΔΔQTcF showed that even at the C_{max} at the highest doses of 800 to 1200 mg the upper 90% CI of the ΔΔQTcF was less than 10 ms in healthy subjects.

Multiple Dose Study 002

Doses of E2027 5 to 400 mg QD × 14 days were well-tolerated in healthy subjects (50 to 85 years of age). Based on the preliminary unblinded safety analysis at 25 to 400 mg QD, the most common TEAEs in non-Japanese subjects (with overall incidence >5%) treated with E2027 were post lumbar puncture syndrome (13.3%), back pain (10%), constipation (10%), headache (10%), dizziness (6.7%) and increased orthostatic HR response (6.7%) (Table 2). Other TEAEs affected only 1 subject across all 5 non-Japanese cohorts. There were no dose-related trends of higher incidence of TEAEs with increasing dose.

In Japanese subjects on 400 mg QD the most common TEAE (affecting >1 subject in the cohort) was constipation. One Japanese subject on E2027 400 mg QD developed a drug rash. The profile of TEAEs was similar between Japanese and non-Japanese subjects on the same dose of 400 mg QD. There were no serious adverse events (SAEs), no severe AEs, and no AEs that required discontinuation of E2027.

Table 2 Incidence of Common Treatment Emergent Adverse Events (>5% Incidence Overall in Part A) in Subjects Administered E2027 or Placebo QD for 14 Days in Study E2027-A001-002

	Placebo		E2027						
TEAE	(N=10) n (%)	Japanese (N=2) n (%)	25 mg (N=6) n (%)	50 mg (N=6) n (%)	100 mg (N=6) n (%)	200 mg (N=6) n (%)	400 mg (N=6) n (%)	400 mg Japanese (N=6) n (%)	Total[a] (N=30) n (%)
Any TEAE	**6 (60.0)**	**2 (100)**	**6 (100)**	**4 (66.7)**	**3 (50.0)**	**5 (83.3)**	**2 (33.3)**	**4 (66.7)**	20 (66.7)
Post lumbar puncture syndrome	0	0	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	0	0	4 (13.3)
Back pain	1 (10.0)	0	1 (16.7)	0	2 (33.3)	0	0	0	3 (10.0)
Constipation	4 (40.0)	0	0	1 (16.7)	1 (16.7)	1 (16.7)	0	2 (33.3)	3 (10.0)
Headache	0	0	1 (16.7)	1 (16.7)	1 (16.7)	0	0	0	3 (10.0)
Dizziness	1 (10.0)	1 (50.0)	2 (33.3)	0	0	0	0	0	2 (6.7)
Orthostatic heart rate response increased	0	0	0	0	0	2 (33.3)	0	0	2 (6.7)

a: Total does not include the E2027 400 mg cohort in Japanese Subjects.

At the time of protocol development, data for orthostatic hypotension by numerical criteria as defined in the protocol (SBP decrease by ≥20 mmHg or DBP decrease by ≥10 mmHg, with increase in HR by ≥20 beats/min) was available in placebo and across doses of E2027 50 to 400 mg QD × 14 days. Treatment emergent (ie, not present at baseline) orthostatic hypotension by numerical criteria occurred in 2 (20%) subjects administered placebo and 8 (26.7%) subjects administered E2027 during the treatment period (Table 3), with similar overall incidence. None of the subjects were symptomatic. Specifically, at steady state from Day 7 to 13, there was 1 subject in E2027 200 mg cohort (Day 10) and 2 subjects in the Japanese E2027 400 mg cohort (1 on Day 11 and 1 on Day 12) who had orthostatic hypotension postdose at ~t_{max}. On Day 14 at 2 hours postdose there was 1 subject in the E2027 200 mg cohort with orthostatic hypotension, but there were no subjects having orthostatic hypotension administered E2027 at other time points during Day 14. Overall the incidence of orthostatic hypotension in subjects administered E2027 was low and occurred at sporadic time points. There were no dose-related trends in the incidence of orthostatic hypotension.

Treatment emergent (ie, not present at baseline) orthostatic tachycardia by numerical criteria (HR increase by >30 beats/min with HR >100 beats/min) without orthostatic hypotension occurred in 3 (30%) subjects administered placebo and 7 (23.3%) subjects administered E2027 during the treatment period, with similar overall incidence. None of the subjects were symptomatic. Specifically at E2027 steady state from Day 7 to 13, there were no subjects with orthostatic tachycardia whether on placebo or E2027 at the time of predose (ie, at C_{min}) and at ~t_{max}. On Day 14 at 4 to 6 hours postdose, there were 1 to 2 subjects affected in the 100 and

400 mg cohorts (both non-Japanese and Japanese), but not at other doses. At other time points on Day 14, there were no subjects administered E2027 with orthostatic tachycardia. Overall, the incidence of orthostatic tachycardia in subjects administered E2027 was low and occurred at sporadic time points. There were no dose-related trends in the incidence of orthostatic tachycardia.

There were 2 subjects in the E2027 200 mg cohort who had TEAEs of increased orthostatic HR response (standing HR increased by >20 beats/min compared to supine) without concomitant orthostatic hypotension, but they were not symptomatic. There was 1 subject in the E2027 200 mg cohort and 1 subject in the Japanese E2027 400 mg cohort who had TEAEs of orthostatic hypotension, but they were not symptoms. In summary, it did not appear that E2027 caused orthostatic hypotension or orthostatic tachycardia.

Table 3 Incidence of Treatment-Emergent Orthostatic Hypotension and Orthostatic Tachycardia At Any Time During Treatment Period in Subjects Administered Doses of E2027 50 to 400 mg or Placebo QD for 14 Days in Study E2027-A001-002

	Placebo		E2027					
	(N=10) n (%)	Japanese (N=2) n (%)	50 mg (N=6) n (%)	100 mg (N=6) n (%)	200 mg (N=6) n (%)	400 mg (N=6) n (%)	400 mg Japanese (N=6) n (%)	Total (N=30) n (%)
Orthostatic hypotension	2 (20.0)	0	0	2 (33.3)	2 (33.3)	1 (16.7)	3 (50.0)	8 (26.7)
Orthostatic tachycardia	3 (30.0)	0	1 (16.7)	3 (50.0)	0	2 (33.3)	1 (16.7)	7 (23.3)

Across the various doses, the mean HR and BP postdose were stable compared to predose. There were no clinically significant changes in ECG parameters and laboratory safety parameters. The incidence of treatment-emergent laboratory safety parameters which were out of normal range across the various cohorts was low and there were no dose-related trends. The mean values of laboratory safety parameters at all time points were similar among subjects treated with placebo and various doses of E2027. It did not appear that E2027 caused changes to vital signs, ECG parameters or laboratory safety parameters compared to placebo.

Preliminary analysis of the PK-QTcF relationship showed that at the plasma E2027 concentrations of the 50 mg QD group, the upper 90% CI of the placebo-corrected change from baseline of the QTcF (ΔΔQTcF) was 3.41 ms (mean 0.71 ms). It also showed that prolongation of the QTcF with upper 90% CI of >10 ms could be excluded at plasma E2027 concentrations up to 2500 ng/mL. This means that at a E2027 dose up to 200 mg QD, there is no prolongation of QTcF with upper 90% CI of >10 ms.

7.1.1.3 Nonclinical Experience (revised per Amendment 05)

To provide supporting evidence for this dose selection on Study 201 it is also proposed that a dose of 50 mg QD administered for 6 weeks in healthy subjects should be investigated to

confirm sustainability of its CSF PD effects. Doses below 25 mg QD are being investigated to explore the dose-PD response relationship across a broader dose range to establish the minimum therapeutic dose for Study 201.

In the monkey cardiovascular (CV) study, the no observed adverse effect level (NOAEL) was 100 mg/kg (C_{max}=2250 ng/mL), and at doses of 300 mg/kg and 1000 mg/kg, E2027 caused an increase in heart rate, prolongation of QTc interval, and a decrease in core body temperature. At 300 mg/kg, heart rate was increased by 15.5% from control value at 1 hour postdose. The QTc interval was prolonged by 5.5% from control value at 2 hours postdose. Body temperature was decreased by 0.20 °C from control value at 2 hours postdose. At 1000 mg/kg, heart rate was increased by 28.7% from control value at 1 hour postdose. The QTc interval was prolonged by 15.0% from control value at 2 hours postdose. Body temperature was decreased by 0.73°C from control value at 2 hours postdose. In the monkey CV study by IV administration, at a dose of 5.4 mg/kg, there were no effects on HR, BP, ECG parameters, or body temperature. At the end of the infusion, the plasma concentration of E2027 was 5770 ng/mL. The highest dose in Study 201 is proposed to be 50 mg QD. The $C_{max,ss}$ of 50 mg QD is within the range of concentrations of E2027 which had no effects on HR, BP, ECG parameters, or body temperature in the monkey CV studies by oral or intravenous dosing.

The toxicity of E2027 has been evaluated in oral repeated-dose toxicology studies of up to 13 weeks duration in rats and cynomolgus monkeys.

In the rat 2-week toxicology study, the NOAEL was 100 mg/kg; and at 1000 mg/kg, the key findings were limited to regenerative changes in the stomach indicative of local irritation, and transient decrease in body temperature. In the monkey 2-week toxicology study, the NOAEL was 30 mg/kg and E2027-related changes were limited to vomiting at 100 and 500 mg/kg, and histologic regenerative changes in the stomach indicative of local irritation at 500 mg/kg.

For the rat 13-week toxicology study, due to polymorphism of CYP2D1, genotyped rats (low--clearance genotype) were used to ensure exposure following oral administration. In the 13-week genotyped rat study, several animals died or sacrificed moribund at 1000 mg/kg/day following up to 3 days and 10 days of treatment in females and males (toxicokinetics group only), respectively, preceded by central nervous system (CNS) related signs including decreased locomotor activity, hypothermia, lateral/prone position, ataxic gait, or bradypnea. The highest dose was reduced to 500 mg/kg in female rats from Day 4 onward; the highest dose of 1000 mg/kg/day was maintained in male rats without further event. In the surviving animals, there were no remarkable clinical signs, although a few episodes of loose stool, decreased activity, and irregular respiration were found in a limited number of males. Low body weight without significant changes in food consumption and slight decreases in red blood cell (RBC) parameters were also observed in males. In histopathology, noteworthy test article-related changes were observed in the stomach in both sexes including hyperplasia/basophilia of neck cells and increased enterochromaffin-like (ECL) cells which was considered to be correlated with an increase in serum gastrin.

In the lower dose groups (30 and 100 mg/kg/day) there were no test article-related changes with exception of salivation likely secondary to the palatability of dosing formulation in a limited number of animals at 100 mg/kg.

Nonclinical findings of note in the 13-week cynomolgus monkey study included vomiting that was observed at 100 mg/kg/day and above in several animals on multiple occasions. A few episodes of drowsiness were also noted in 2 females treated at 500 mg/kg. At 30 mg/kg, there were no test article-related changes.

In the 13-week toxicology studies, the NOAEL was 100 and 30 mg/kg in rats and monkeys, respectively.

HP4, mono-hydroxylated E2027, is a potential disproportionate metabolite in humans. Study E2027-A001-005 (Study 005: An Open-Label, Single-Dose Study to Determine the Metabolism and Elimination of [^{14}C]E2027 in Healthy Male Subjects) has been recently completed. Preliminary results of metabolite composition in plasma obtained from Study 005 indicated that parent E2027 was the major component with 62.5% of total plasma radioactivity ($AUC_{(0\text{-}96h)}$), and HP4 was 6.3% of total plasma radioactivity ($AUC_{(0\text{-}96h)}$). HP4 exposure was detected at only trace levels at the highest doses tested in rats and monkeys in chronic toxicology studies.

E2027 as well as HP4 were negative in Ames tests. As exposure of HP4 was at trace levels only in previous studies in rats and monkeys, toxicological evaluation in mice was conducted as a combination treatment of E2027 and HP4.

E2027 was administered orally once a day for 4 weeks to male and female non-Tg rasH2 mice at a dose of 600 mg/kg alone or at a dose of 200, 400, or 600 mg/kg with HP4 given at a common dose of 20 mg/kg. There were testicular changes in all treated groups, which was characterized by degeneration of the seminiferous epithelium associated with decreased testicular weight. Spermatogonia appeared to be unaffected on histopathology, suggesting that the testicular changes are likely to be reversible. There was no dose dependency in testicular findings among groups given the same dose of HP4 and different doses of E2027 (600/20, 400/20, and 200/20 mg/kg groups, E2027/HP4 dose, respectively). In mice dosed only with E2027 (600/0 mg/kg group), the incidence and severity of testicular changes were slightly lower than the other groups.

There were no testicular changes in the repeated-dose toxicity studies in rats (up to 26 weeks) or monkeys (up to 39 weeks).

These results suggest that, although possible involvement of both E2027 and HP4 cannot be completely ruled out, HP4 is likely playing a greater role than E2027 in the induction of testicular toxicity. Testicular toxicity was detected in non-Tg rasH2 mice at E2027 exposure multiple of 3.8-fold and at about 0.4 fold exposures of HP4 relative to the exposure of E2027 and HP4, respectively, in humans treated with E2027 at 50 mg.

7.2 Study Rationale

Cyclic nucleotides such as cyclic adenosine monophosphate (cAMP) and cGMP work as second messengers in the intracellular signaling cascade, and play a critical role in learning and memory function in animal models (Domek-Łopacińska and Strosznajder, 2005). Cyclic GMP is involved in the induction of hippocampal long-term potentiation (LTP) that is considered to be a neural substrate of cognitive function. In the synaptic region, activation of N-methyl-D-aspartate (NMDA) receptors leads to nitric oxide synthase (NOS) activation via Ca^{2+} influx. This is followed by activation of guanylyl cyclase (GC) by NO in both pre- and postsynaptic regions. Subsequently, second messenger cGMP is synthesized from guanosine triphosphate (GTP) by GC. cGMP activates cGMP-dependent protein kinase (PKG) and cyclic nucleotide-gated cation channels (CNGCs). PKG phosphorylates various proteins and induces diverse physiological effects which are involved in synaptic plasticity. Therefore, increase of cGMP in synaptic regions is expected to enhance LTP and consequently improve cognitive function. Phosphodiesterases (PDE) hydrolyze cGMP by breaking the phosphodiester bond with guanosine monophosphate; thus, inhibition of PDE constitutes a mechanism whereby levels of cGMP can be increased.

In in vivo behavioral studies, inhibitors of NOS and GC are reported to impair cognitive function, while GC activators, cGMP analogues, and PDE inhibitors enhance it. Therefore, compounds that enhance the NO-cGMP cascade are likely to improve cognitive function. PDE9 is a cGMP-degrading enzyme and expressed in brain, and its inhibitor is thought to increase neuronal cGMP and enhance cognitive function. Therefore PDE9 inhibitors may be efficacious in neurodegenerative diseases with cognitive impairment such as LBD and AD. Subjects with AD have reduced CSF cGMP compared to healthy subjects and a PDE9 inhibitor which increases CNS cGMP may be specifically useful in AD and neurodegenerative diseases which have concomitant amyloid pathology similar to AD such as in DLB (Donaghy, et al., 2015). E2027 is a highly potent, selective, and orally available PDE9 inhibitor, which is being developed as a treatment for cognitive deficit in AD or LBD. E2027 inhibits PDE9 with a 50% inhibitory concentration (IC_{50}) of 3.5 nM and has more than 1000-fold selectivity over other enzymes of the PDE family. Oral administration of E2027 significantly elevated CSF (sampled at ~t_{max} postdose) and hippocampal cGMP by 200% and 20%, respectively, in rat, and at the same dose improved object recognition memory. It was also found that in animal cognition models E2027 improved cognition when administered alone or concurrently with donepezil. In the head twitch response animal model which represented a hyperserotoninergic behavior, E2027 reduced the number of head twitches, suggesting that it may also improve some of the neuropsychiatric symptoms in DLB (Study No. TP_DOI002_Mar2016). Thus, E2027 may improve cognition in DLB and AD via mechanistic pathways not directly involving cholinergic neurotransmission.

7.2.1 Study Overview

The proposed study (E2027-G000-201; Study 201) is a Phase 2, randomized, double-blind, placebo-controlled study to determine the superiority of a dose of E2027 (50 mg QD) compared to placebo on various cognitive and neuropsychiatric endpoints in subjects with DLB. Study 201 will also evaluate the safety, tolerability, PK, and PD effects of E2027.

Subjects with mild to moderate dementia due to DLB as diagnosed by established international guidelines are eligible. In Study 201 subjects are eligible if they are not already established on AChEI and/or memantine (ie, naïve to standard treatment) or if they have been on a stable dose of an AChEI and/or memantine for at least 12 weeks before Screening. (revised per Amendment 03) Cognitive and neuropsychiatric assessments will be performed at Screening and Baseline. Eligible subjects will be randomly assigned to placebo or a dose of E2027 (in a ratio of 1:1) for a Treatment Period of 12 weeks, during which efficacy and safety assessments will be conducted. Randomization will be stratified by whether a subject is naïve to AChEI or established on a stable dose of AChEI and by geographical region (North America, EU, and Japan). Up to approximately 20% of randomized subjects will be on memantine. (revised per Amendment 04) A follow-up visit will take place 4 weeks after the final dose of study drug. The rationale for selection of one dose of E2027 (50 mg QD) is discussed in Section 9.4.4.

The first primary efficacy endpoint (on cognition) will be the Montreal Cognitive Assessment (MoCA), which is a comprehensive cognitive endpoint evaluating various cognitive domains. The choice of the MoCA as primary endpoint is discussed in Section 9.2. The coprimary efficacy endpoint on global clinical status will be the Clinician's Interview Based Impression of Change Plus Caregiver Input (CIBIC-Plus). The use of both coprimary endpoints (1 on cognition and 1 on global clinical status) is consistent with regulatory guidelines for clinical trials in dementia such that if E2027 shows positive results on both coprimary endpoints, the study may be considered as a pivotal study in future regulatory submissions. For proof of concept (POC) purposes, the minimum requirement is that E2027 shows benefit on the cognitive endpoint (MoCA).

Secondary endpoints include the Neuropsychiatric Inventory (NPI), Mini-Mental State Examination (MMSE), Cognitive Fluctuation Inventory (CFI), and Clinical Global Impression of Change in Dementia with Lewy Bodies (CGIC-DLB). Exploratory endpoints include Scales for Outcome in Parkinson's disease—Sleep (SCOPA-Sleep) and percentage change from baseline of CSF cGMP (in subset of subjects who volunteer to undertake CSF sampling by lumbar puncture).

7.2.2 Risk-Benefit Summary (revised per Amendments 02 and 05)

DLB is the proposed disease for this Phase 2 study given the limited range of current cognitive treatments in this disease. Given that current treatments (AChEI) for cognitive impairment in DLB typically achieve an improvement in MMSE by 1.5 to 3 points (McKeith, et al., 2000; Mori, et al., 2012; Ikeda, et al., 2015), with MMSE on treatment with AChEI typically at 23 points (Biundo, et al., 2016), there is room for further improvement of cognitive function in DLB compared to normal (MMSE >26).

In subjects treated with 50 mg QD for 6 weeks it was found that the CSF cGMP increased from baseline by 229% on Day 13 and by 222% on Day 41. Thus the CSF PD effects were sustained over a treatment period of up to 6 weeks in subjects administered E2027 50 mg QD. The E2027 dose proposed in Study 201 of 50 mg QD is expected to achieve pharmacodynamics effects in CSF cGMP elevation from baseline by approximately 200% or more sustained throughout a dosing interval during chronic treatment with E2027. The proposed dose in Study 201 is

expected to achieve similar PD effects in CSF cGMP as in animal models with cognitive enhancement. Therefore, E2027 at 50 mg QD may show efficacy in cognition (increase in MoCA and MMSE scores) and possibly neuropsychiatric symptoms (reduction in NPI scores) in subjects with DLB.

This dose of E2027 at 50 mg QD in Study 201 also has a safety margin of at least 2-fold relative to the exposure at the NOAEL dose in the 13-week toxicology studies in the most sensitive species. The recent study in mice of the HP4 metabolite indicated that the HP4 metabolite is likely to be playing a role in testicular changes in mice. This occurred under the exposure of E2027 which was 3.8-fold the exposure in humans at 50 mg QD in the multiple ascending dose study (Study 002). On the other hand, the testicular effects of HP4 occurred at mouse exposure which was 0.4-fold the concurrent human exposure (at E2027 50 mg in Study 005). Although chronic treatment was not associated with testicular changes in rats and monkeys up to 26 or 39 weeks, the human effect is yet to be evaluated.

Based on the Phase 1 clinical studies conducted to date, the proposed dose of E2027 at 50 mg QD is expected to be well-tolerated without causing clinically significant changes in vital signs, ECG parameters and laboratory safety parameters. Adverse events which were reported with E2027 include dizziness, headache, dry mouth, neck pain, postural orthostatic tachycardia, insomnia, skin rash, muscle stiffness, paresthesia, nausea, vomiting, lower abdominal pain, anxiety and restless legs. These adverse events were mild to moderate.

Study 201 was initiated before the effects of HP4 metabolite in mice with testicular changes were known. Given the CSF PD effects, well-tolerated clinical safety profile, and safety margin of the dose of E2027 in Study 201 relative to the NOAEL in the chronic rat and monkey toxicology studies, the sponsor considers that the risk-benefit balance is favorable for the investigation of E2027 in subjects with DLB at the proposed dose of 50 mg QD for 12 weeks. In view of the new findings of testicular changes in mice associated with the HP4 metabolite, the sponsor considers that because DLB is a progressive neurodegenerative condition with limited treatment options, the mean age of male subjects already randomized is 74 years old (range 55 to 85), and treatment duration of 12 weeks, male subjects already randomized in the study can continue under the risk management procedures proposed in Amendment 05 (see Section 9.4.7.3).

8 STUDY OBJECTIVES

8.1 Primary Objectives

- To determine whether E2027 is superior to placebo on the cognitive endpoint of MoCA in subjects with DLB after 12 weeks of treatment
- To determine whether E2027 is superior to placebo on the global clinical endpoint of CIBIC-Plus after 12 weeks of treatment

8.2 Secondary Objectives

(Order of secondary objectives revised per Amendment 05)

- To determine whether E2027 is superior to placebo on the following secondary endpoints after 12 weeks of treatment:
  - Clinician Global Impression of Change in Dementia with Lewy Bodies (CGIC-DLB)
  - Cognitive Fluctuation Inventory (CFI)
  - Mini-Mental State Examination (MMSE)
  - Neuropsychiatric Inventory (NPI)
- To evaluate the safety and tolerability of E2027 in subjects with DLB
- To characterize the population pharmacokinetics (PPK) of E2027 in subjects with DLB, including evaluation of the effects of intrinsic and extrinsic factors on E2027 PK

8.3 Exploratory Objectives

- To explore the efficacy of E2027 compared to placebo on the following endpoints after 12 weeks of treatment:
  - Scales for Outcome in Parkinson's disease-Sleep (SCOPA-Sleep)
  - Dementia-related quality of life as assessed by the Dementia Quality of Life Measure (DEMQOL; interview of subject) and Dementia Quality of Life Measure by Proxy (DEMQOL-Proxy; interview of caregiver or informant about subject)
  - General health status as assessed by the EuroQol- 5 Dimension questionnaire (EQ-5D; completed by subject) and EuroQol- 5 Dimensions questionnaire by Proxy Version 1 (EQ-5D Proxy; caregiver or informant completion of report about subject)
- To evaluate the relationship between PK exposure of E2027 and its effects on various efficacy and safety endpoints
- To explore the PK/PD relationship between the exposure of E2027 in CSF/plasma and its effects on CSF PD biomarker endpoints, including CSF cGMP, if data permit
- To explore the relationship between the E2027 PD effects (including CSF cGMP) with E2027 effects on various efficacy endpoints, if data permit
- To explore collected pharmacogenomic (PGx) samples by investigating heterogeneity in clinical features of disease, including differences in baseline characteristics as well as response to compound (efficacy, safety and/or absorption, distribution, metabolism, and excretion [ADME]). These exploratory analyses are not limited to this protocol or project. These findings may be used for identification and validation of new drug targets.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicentre, randomized, double-blind, placebo-controlled, parallel-group study in subjects with dementia with Lewy bodies (DLB) who will be treated with placebo or a dose of E2027 (50 mg QD) for 12 weeks. An overview of the study design is presented in Figure 1.

In some of the countries selected for this study, donepezil is approved for DLB, with AChEI and increasingly memantine often used as part of standard care in patients with DLB. Therefore, the study design allows for add-on therapy to standard of care for DLB, which includes AChEI and/or memantine at stable doses, except for any prohibited medications specified in this protocol. Subjects who are not receiving AChEI and/or memantine are also eligible, but are not permitted to start such medications during the study. (revised per Amendment 03) Randomization will be stratified based on whether subjects are on a stabilized dose of AChEI or not and by geographical region (ie, North America, Europe, Japan). Up to approximately 20% of randomized subjects will be on memantine. (revised per Amendment 04) Subjects will be randomized to placebo and a dose of E2027 (50 mg QD) in a ratio of 1:1.

For all subjects study participation will comprise 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last for up to 6 weeks and will include a Screening Period (up to 5 weeks) and a Baseline Period (1 week). The Randomization Phase will last for 16 weeks and will include a Treatment Period (12 weeks) and a Follow-up Period (4 weeks).

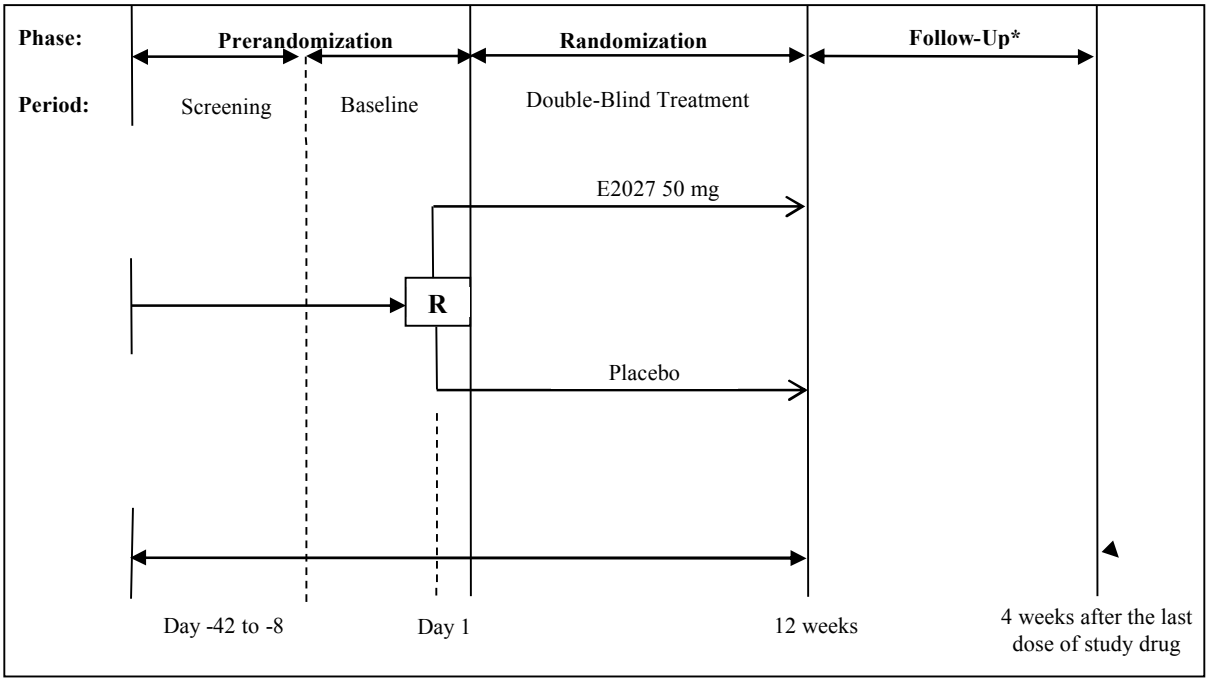

Figure 1 Study Design for Study E2027-G000-201

*Subjects will have follow-up 4 weeks after the end of the treatment and a final assessment completed.
R = randomization

9.1.1 Screening Period

Screening will occur between Day -42 and Day -8. 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 before the conduct of any

screening procedures or assessments. All subjects will be assessed for eligibility through review of medical history, physical examination (including neurological examination), laboratory tests, vital signs and electrocardiograms (ECGs). They will be assessed on clinical scales of cognition and depression, safety magnetic resonance imaging (MRI of the brain) and dopamine transporter (DAT) brain imaging or myocardial scintigraphy ([^{123}I]meta-iodobenzylguanidine [MIBG]) (if indicated in individual subjects and not previously performed) to confirm that they meet the diagnostic criteria and severity for DLB. Their motor features will be assessed on the Movement Disorders Society (MDS) Unified Parkinson's Disease Rating Scale Part III: Motor Examination (UPDRS-III) and staged by the Hoehn and Yahr Scale (HYS). Their history of suicidality will be assessed by the Columbia Suicide Severity Rating Scale (C-SSRS). They will also be assessed regarding other medical conditions and concomitant medications to ensure that these are stable with no changes to treatment required and that they do not interfere with their safety or study procedures.

Eligibility assessments at Screening will be conducted in tiers and subjects will need to satisfy eligibility criteria in each tier before proceeding to the next tier. In Tier 1 demographics, medical history (including history of DLB and other medical conditions) and concomitant medications will be reviewed. In Tier 2, clinical assessments on cognition and depression will be conducted in the morning (whenever possible) in subjects in the following order: MMSE and Geriatric Depression Scale (GDS) should be done first, followed by the MoCA and SCOPA-Sleep. The caregivers or informants will also complete the Short Fluctuation Questionnaire (SFQ), CFI and the NPI. If the eligibility criteria regarding the MMSE and GDS are not met, the other procedures (MoCA, SCOPA-Sleep, SFQ, CFI and NPI) do not have to be performed and the subject should be screen failed. In Tier 3 subjects will be assessed with the Modified Hachinski Ischemic Scale, UPDRS-III, HYS and C-SSRS. In Tier 4 subjects will undertake physical examination, vital signs, ECG and clinical laboratory tests. In Tier 5, subjects will be assessed by safety MRI for brain abnormalities that may affect eligibility. In Tier 6, if indicated as judged by the investigator, individual subjects may also undertake DAT brain imaging scan or myocardial MIBG scan to help establish their diagnosis. It is recommended that where appropriate Tiers 1 to 4 should be performed on the same day and Tiers 5 and 6 on a separate day. However, the investigator may perform the various tiers on separate days as appropriate for each subject. The scores of various clinical scales (including NPI, SFQ, and UPDRS-III) and cognitive tests (MMSE, MoCA) at Screening will be reviewed by a central process. Subjects who are diagnosed by the investigator with DLB but whose scores on clinical scales or cognitive tests are found not to be consistent with the diagnosis during central review will be discussed with the investigator to determine their eligibility.

Due to the intrinsic variability of cognitive functions in DLB, subjects who screen fail at Tier 2 may be rescreened after at least 30 days, but as a guide, rescreening frequency should not be more frequent than once every 4 months and a subject should not be rescreened more than 2 times under the same version of the eligibility criteria. Subjects who are deemed eligible after passing all tiers at Screening will proceed to the Baseline Visit.

9.1.2 Baseline Period

The Baseline Visit may take place at any time up to 7 days before the first dose of study drug (Day 1, ie, during Day -7 to Day -1, but should take place at least 2 weeks after the Screening Visit Tier 2 assessments). In subjects who had DAT brain imaging scan or MIBG scan during Screening, the Baseline Visit must take place at least 1 week after the scan. Study assessments should be conducted in the morning (whenever possible). Cognition will be assessed by the MoCA, which should be the first clinical scale to be administered before any invasive procedures. It is recommended that after the MoCA the following efficacy assessments in subjects should be performed in the following overall order (other study assessments may be conducted in between these efficacy assessments): Clinician Interview Based Impression of Severity plus Caregiver Input (CIBIS-Plus) and SCOPA-Sleep. The subject will be interviewed to complete the DEMQOL. The EQ-5D will be self-administered and completed by the subject. The caregiver or informant will also complete the CIBIS-Plus, NPI, CFI, EQ-5D Proxy Version 1 and will be interviewed to complete the DEMQOL-Proxy. The rater administering the CIBIS-Plus should be independent of the rater(s) who administer the other clinical scales.

At Baseline Visit subjects will be assessed regarding other medical conditions and concomitant medications (including medications for DLB) to ensure that these remain stable with no changes to treatment required and that they do not interfere with their safety or study procedures. Other safety assessment including vital signs, ECGs, laboratory tests and C-SSRS will also be conducted. The results of clinical laboratory tests at the Baseline Visit must be reviewed by the investigator in accordance with Exclusion Criterion 17 before proceeding to randomization, unless these tests showed no clinically significant out of range values at Screening.

9.1.3 Randomization Phase/Treatment Period

After completing study assessments at the Baseline Visit, subjects who continue to be eligible will proceed to the Randomization Phase, and will be randomized to placebo or E2027 (50 mg QD). They will be provided with study drug (placebo or E2027) to start administration in the morning of Day 1 at home. They will continue to take study drug for 12 weeks. During the Treatment Period study visits will be conducted after 2, 4, 6, 9 and 12 weeks on study drug. Safety assessments will be conducted at all these visits. Efficacy assessments will be performed after 6 and 12 weeks on study drug and should be performed at approximately the same time of the day as at the Baseline Visit whenever possible (preferably in the morning). The MoCA should be the first clinical scale to be administered before any invasive procedures. As far as is possible a subject should have the same rater administering the MoCA throughout his/her participation in the study. It is recommended that other efficacy assessments in subjects should be performed in the following overall order (other study assessments may be conducted in between these efficacy assessments): CIBIC-Plus, MMSE (after 12 weeks only) and SCOPA-Sleep. As far as is possible a subject should have the same rater administering the CIBIS/C-Plus throughout his/her participation in the study. The rater administering the CIBIC-Plus should be independent of the rater(s) who administer the other clinical scales. The subject will self-complete the EQ-5D. The caregiver or informant will also complete the CIBIC-Plus,

NPI, CFI, and EQ-5D Proxy Version 1. In addition at the study visit after 12 weeks on study drug interviews with the subject and the caregiver or informant will be conducted to complete the DEMQOL (subject) and DEMQOL-Proxy (caregiver or informant). Safety assessments will be conducted at these visits, including review of adverse events (AEs), vital signs, ECG, laboratory safety tests, C-SSRS and UPDRS-III. The investigator will review all the efficacy endpoints and safety data at the visits after 6 weeks and 12 weeks on study drug and formulate the CGIC-DLB of the subject's clinical status from Baseline.

9.1.3.1 CSF Substudy

A subset of subjects will participate in a substudy in which CSF will be collected by LP during Screening and again during the Randomization Phase after 9 weeks of treatment on study drug. Participation in the substudy will be voluntary. After they have completed all screening assessments and are deemed eligible for the study, a baseline CSF sample will be collected at least 7 days before the Baseline Visit. If necessary, in these subjects the Screening Period may be extended by 1 week after discussion with the sponsor medical monitor. After they have completed 9 weeks of treatment, they will have a 2nd CSF sample collected. The CSF samples will be collected in the morning at approximately the same time, either in the fasted state (preferred) or at least 2 hours after breakfast.

As data permit, CSF cGMP will be assayed to evaluate the PD effects of E2027 in these subjects with DLB. Other CSF PD biomarkers related to DLB or E2027 PD effects may also be assayed if appropriate. CSF E2027 concentrations will also be determined.

9.1.4 Follow-Up Period

After the Treatment Period, subjects will undertake a Follow-Up Visit 4 weeks after the final dose of study drug. Efficacy assessments should be performed at approximately the same time of the day as at the Baseline Visit whenever possible (preferably in the morning). The MoCA should be the first clinical scale to be administered before any invasive procedures. It is recommended that other efficacy assessments in subjects should be performed in the following overall order (other study assessments may be conducted in between these efficacy assessments): MMSE and SCOPA-Sleep. The caregiver or informant will also complete the CFI and NPI. Safety assessments will also be completed.

The end of study is defined as the last subject completing the Follow-Up Visit.

Subjects who prematurely discontinue study drug for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their last dose of study drug. The safety and efficacy assessments normally performed after 12 weeks of treatment will be conducted at the ED Visit. In addition, subjects who discontinue study drug are expected to continue in the study for the originally scheduled visits, starting with the next such visit that is >7 days after the ED Visit. Subjects who prematurely discontinue the study should attend at least 1 originally scheduled visit after the ED Visit.

9.1.5 Data Safety Monitoring Board

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the study is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

9.2 Discussion of Study Design, Including Choice of Control Groups

This is randomized, double-blind, placebo-controlled POC study to evaluate the efficacy and safety of E2027 in subjects with DLB. Randomization will be used to avoid bias in the assignment of subjects to treatments. Stratification will be used to ensure that baseline characteristics which may affect treatment response (whether subjects are established on AChEI or not and by region) are balanced across treatment groups and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce bias during evaluation of efficacy and safety endpoints.

This study selects DLB within the LBD spectrum for the following reasons: (1) as the first POC study having only DLB subjects, it ensures a relatively more homogeneous population and reduces variability compared to having a broad mixture of DLB and PDD subjects, which optimizes the probability of detecting cognitive efficacy; (2) DLB subjects have higher incidence of concomitant amyloid pathology similar to AD and therefore may have similar changes in the cGMP pathways as in AD, so the pharmacological mechanism of E2027 may be more likely to show efficacy in DLB, making DLB more attractive for this stage of clinical development.

A meta-analysis of efficacy in clinical trials of AChEI in PDD and DLB suggested comparable efficacy effect size in both diagnostic categories (Matsunaga, et al., 2015), which makes it plausible that a new drug with efficacy in DLB may also be efficacious in PDD (or vice versa). Therefore, if E2027 is efficacious in DLB in Study 201 it will support extending its indications to PDD in the LBD spectrum in phase 3 clinical development.

AChEIs are the current standard treatments for LBD (Walker, et al., 2015; McKeith, et al., 2017; UK National Institute for Health and Care Excellence [NICE] guideline, 2018); as such, subjects who are established on a stable dose of AChEIs are eligible. There is also some evidence of overall clinical benefit of memantine in treatment of DLB although the benefit on cognition was small (Aarsland, et al., 2009), and increasingly it is also used as part of standard treatment in some national guidelines (eg, UK NICE guideline, 2018). As not all subjects will receive AChEI and/or memantine as standard care, subjects who are naïve to AChEI or memantine are also eligible. Studies in animal models indicate that E2027 may improve cognition either as monotherapy or in combination with an AChEI or memantine. This supports the enrollment of subjects with or without concomitant AChEI and/or memantine treatment. Previous studies showed that the efficacy of rivastigmine or donepezil in PDD or

DLB reached maximum effect after at least 12 weeks of treatment (Dubois, et al., 2012; Mori, et al., 2012). Similarly, previous studies with memantine suggested some efficacy on global clinical endpoints after 12 weeks of treatment (Aarsland, et al., 2009). Therefore, all subjects who are already taking AChEIs or memantine will be required to be on a stable dose for at least 12 weeks before Screening. The design of Study 201 which permits subjects with/without concomitant use of AChEI was also used in a previous study with memantine in subjects with LBD (Aarsland, et al., 2009). (revised per Amendment 03)

Previous studies showed that AChEIs demonstrated efficacy in PDD or DLB after 12 weeks of treatment. It is considered that this is a reasonable clinical expectation for onset of efficacy and therefore the treatment duration is set to 12 weeks in Study 201.

Subjects are diagnosed with DLB as per the 4th report of the DLB Consortium (McKeith, et al., 2017), which is recommended by EMA guidelines. In previous studies of donepezil in DLB conducted by Eisai, it was found that subjects with visual hallucinations at baseline showed better efficacy. Therefore, in this study subjects are required to have visual hallucinations to be eligible.

There are 2 coprimary endpoints which include a cognitive endpoint and a global clinical endpoint as recommended by regulatory guidelines for clinical trials on dementia. The primary endpoint on cognition is the MoCA, which is a composite cognitive endpoint evaluating various domains including attention, memory, executive function and visuospatial abilities. It has greater emphasis on executive functions, attention and visuospatial abilities known to be impaired in DLB and PDD (Biundo, et al., 2016) than MMSE. MoCA is less likely to show ceiling effect and is more sensitive in detecting early cognitive change in DLB than MMSE (Biundo et al., 2016). It showed similar rate of cognitive decline with MMSE in 1-year follow-up of DLB patients (Biundo et al., 2016). Moreover, it showed treatment benefit on cognition in a clinical trial of rivastigmine in PDD, indicating sensitivity to treatment effects of cognitive enhancing drugs (Li, et al., 2015). The coprimary endpoint on global clinical status is the CIBIC-Plus which evaluates global clinical impression of change from baseline by an independent rater who determines change in clinical status solely based on interview with the subject and caregiver or informant without reviewing efficacy and safety data obtained postrandomization. It showed overall clinical benefit in subjects treated with donepezil with PDD (Dubois, et al., 2012) and DLB (Mori, et al., 2012). The use of both coprimary endpoints (one on cognition and one on global clinical status) is consistent with regulatory guidelines for clinical trials in dementia such that if E2027 shows positive results on both coprimary endpoints, the study may be considered as a pivotal study in future regulatory submissions. Thus, in this study E2027 (50 mg QD) has to show statistically significant benefit on both the MoCA and the CIBIC-Plus for E2027 compared to placebo. If this is not achieved, but E2027 (50 mg QD) shows statistically significant benefit on at least the MoCA, then the result is considered positive for POC, but not a positive pivotal study, and additional pivotal studies will be conducted.

Other cognitive endpoints, including MMSE and CFI, are secondary endpoints. The MMSE is commonly used in clinical practice to document subjects' cognitive status and showed efficacy with donepezil in PDD (Dubois, et al., 2012) and DLB (Mori, et al., 2012; Ikeda, et

al., 2015). The use of MMSE as a secondary efficacy endpoint on cognition allows benchmarking of the efficacy of E2027 with other precognitive drugs in these indications. The CFI evaluates within subject fluctuation of cognitive symptoms and it showed treatment benefit with donepezil in subjects with DLB (Mori, et al, 2012).

The NPI evaluates behavioral and psychiatric features in subjects with dementia and it showed benefit in subjects treated with rivastigmine in PDD (Burn, et al., 2006) and in subjects treated with donepezil in DLB (McKeith, et al., 2000; Mori, et al., 2012). It is therefore used as one of the secondary efficacy endpoints in Study 201 to evaluate efficacy on non-cognitive features.

Sleep disturbance is common in PDD and DLB (Boddy et al, 2007). The effects of E2027 on sleep in animal models were not specifically evaluated. In Study 201 the effects of E2027 on sleep will be evaluated with the Scales for Outcome in Parkinson's disease—Sleep (SCOPA-Sleep) which will be an exploratory efficacy endpoint. This scale showed improvement in sleep quality in subjects with Parkinson's disease psychosis who were treated with pimavanserin (Cummings, et al., 2014).

The CGIC-DLB provides an overall clinician-determined summary measure of change from the subject's clinical status at Baseline Visit that takes into account all available information from the efficacy endpoints above (which include cognitive function, non-cognitive symptoms, behaviour and the impact of the symptoms on the patient's ability to function) and safety data. The CGIC-DLB is scored by the investigator and is separate from the evaluation with the CIBIC-Plus by an independent rater. A similar CGIC endpoint was used in a previous study in subjects with AD (Grove, et al., 2014).

9.3 Selection of Study Population

Approximately 260 subjects will be screened to provide a maximum of 182 randomized subjects. Allowing for a 12% dropout rate, it is anticipated that 160 randomized subjects will complete the study. Subjects will be enrolled at approximately 70 sites in North America, Europe, and Japan.

Participation in the CSF substudy is voluntary. It is estimated that approximately 30% of subjects will participate in the CSF substudy.

9.3.1 Inclusion Criteria

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

1. Male or female, age 50 to 85 years, inclusive at time of consent.
2. Meet criteria for probable DLB (as defined by the 4th report of the DLB Consortium [McKeith, et al., 2017]) (Appendix 1). Specific situations regarding the use the imaging are described below:

a. have 1 core clinical feature only by the investigator and who did not have previous reports of DAT brain imaging scan, MIBG scan or polysomnography (PSG) will undertake DAT brain imaging scan or MIBG scan as organized by the investigator.
b. have 2 or more core clinical features by the investigator but who are judged as having only 1 core clinical feature by central reviewer and who did not have previous reports of DAT brain imaging scan, MIBG scan or PSG may undertake DAT brain imaging scan or MIBG scan after discussion with the sponsor medical monitor.
c. have 2 or more core clinical features by the investigator and the central reviewer and who did not have previous reports of DAT brain imaging scan, MIBG scan or PSG may undertake DAT brain imaging scan or MIBG scan after discussion with the sponsor medical monitor if the investigator considers that imaging is necessary to confirm the diagnosis.

Where there are local/national regulatory requirements for additional central regulatory review of radiation exposure for the use of DAT / MIBG scans, enrollment of subjects is restricted to those who do not require a new DAT / MIBG scan conducted under this study (ie, subjects who have historical DAT/MIBG scan/PSG results, or subjects who have 2 core clinical features of DLB) until such approval is granted by the regulatory authority on radiation exposure. Thereafter enrollment of subjects will extend to those who may require a new DAT / MIBG scan under this study. (revised per Amendment 01)

3. MMSE $\geq$14 and $\leq$26 at Screening Visit.
4. Has experienced visual hallucinations during the past 4 weeks before Screening Visit.
5. If receiving AChEIs, must have been on a stable dose for at least 12 weeks before Screening Visit, with no plans for dose adjustment during the study. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs from Screening to the end of the study.
6. If receiving memantine, must have been on a stable dose for at least 12 weeks before Screening Visit, with no plans for dose adjustment during the study. Treatment naïve subjects can be entered into the study but there should be no plans to initiate treatment with memantine from Screening to the end of the study. (revised per Amendment 03)
7. 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, not be suffering from cognitive impairment, be sufficiently familiar with the subject and 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 should normally be residing with 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. As a guide the caregiver or informant should have contact with the subject on at least 4 days a week and each day for a total of at least 5 hours. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At all visits caregivers or informants need to attend the visit in person along with the subject. If

during the study, the designated caregiver or informant relinquishes his/her responsibilities as caregiver, a replacement caregiver or informant who meets the criteria above and who has similar knowledge of the subject's clinical status from Baseline throughout the Treatment Period must be found. If no such replacement caregiver or informant is available, the subject must be discontinued from the study.

8. Provide written informed consent. If a subject lacks capacity to consent in the investigator's opinion, the subject's assent should be obtained, as required in accordance with local laws, regulations and customs, plus the written informed consent of a legal representative should be obtained (capacity to consent and definition of legal representative should be determined in accordance with applicable local laws and regulations). In countries where local laws, regulations and customs do not permit subjects who lack capacity to consent to participate in this study, they will not be enrolled (revised per Amendment 02).

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 those caused by the subject's DLB, including any comorbidities detected by clinical assessment or MRI.
2. History of transient ischemic attacks or stroke within 12 months of Screening.
3. Modified Hachinski Ischemic Scale >4.
4. Parkinsonian (extrapyramidal) features with Hoehn & Yahr stage IV or higher.
5. Any major psychiatric diagnosis, including schizophrenia, bipolar disorder and current major depressive disorder as per Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V).
6. GDS score >8.
7. Severe visual or hearing impairment that may interfere with the subject study assessments including cognitive testing.
8. History of deep brain stimulation or other neurosurgical procedure for Parkinson's disease.
9. Have thyroid stimulating hormone (TSH) above 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 whether or not they are taking thyroid supplements.
10. Abnormally low serum Vitamin B12 levels (less than the lower limit of normal [LLN]) for the testing laboratory (if subject is taking Vitamin B12 injections, level should be at or above the LLN for the testing laboratory).
11. Contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or positron emission tomography (PET) scanning as per local guidelines need not be excluded.
12. Evidence of other clinically significant lesions that suggest a dementia diagnosis other than DLB on brain MRI at Screening. All MRIs will be acquired using a standardized procedure

that will be outlined in the Imaging Charter and Imaging Acquisition Guidelines (IAG) and will be read by an approved centralized reader.

13. Other significant pathological findings on brain MRI at Screening, including but not limited to: any macrohemorrhage (greater than 10 mm at greatest diameter); an area of superficial siderosis; evidence of cerebral contusion, encephalomalacia, aneurysms, arteriovenous 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 or equal to 1 cm at their greatest diameter need not be exclusionary)
14. Hypersensitivity to E2027 or any of the excipients.
15. A prolonged QTcF as demonstrated by triplicate ECG at the Screening or Baseline Visit (ie, mean value >450 msec).
16. Had symptomatic orthostatic hypotension or symptomatic orthostatic tachycardia which resulted in hospitalization or urgent medical review in hospital in the past 12 months before Screening.
17. Any other clinically significant abnormalities which in the opinion of the investigator, require further investigation or treatment or which may interfere with study procedures or safety in the following:
    - Physical examination, ECG, vital signs at Screening or Baseline Visit
    - Laboratory tests at Screening Visit
18. Malignant neoplasms within 3 years of Screening (except for basal or squamous cell carcinoma of the skin, or localized prostate cancer in male subjects). Subjects who had malignant neoplasms but who have had at least 3 years of documented uninterrupted remission before Screening need not be excluded.
19. Has a "yes" answer to C-SSRS suicidal ideation Type 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.
20. 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 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.
21. Any other medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) which are not stably and adequately controlled, or which in the opinion of the investigator may affect the subject's safety or interfere with the study assessments.
22. Taking any of the prohibited medications or not meeting the requirements regarding stable doses of permitted medications.
23. Participation in a clinical study involving any investigational drug/device for DLB within 6 months before Screening or any other investigational drug/device in the 8 weeks or 5 half-lives (whichever is longer) of the study medication before Screening unless it can be documented that the subject was in a placebo treatment arm.

24. Planned surgery which requires general, spinal or epidural anesthesia that will take place during the study. Planned surgery that requires only local anesthesia and can be undertaken as a day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.
25. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]). 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.
26. Females of childbearing potential (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]).
27. For subjects who participate in the CSF substudy, the following exclusions apply:
    - A bleeding disorder that is not under adequate control (including a plate count <50,000, international normalized ratio [INR] >1.5 or partial thromboplastin time [PTT] > upper limit of normal [ULN]).
    - Any contraindications to lumbar puncture (LP) (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, or obesity to the extent that it makes LP technically difficult).

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.

A subject who discontinues study treatment should be followed for subsequent protocol-specified visits and procedures. If a subject discontinues study drug(s) but remains in the study, the set of end-of-treatment procedures will be administered, and follow-up information will be collected. The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatments Administered

The following treatments will be administered to subjects in this study (Table 4).

Table 4 Treatments Administered

Drug Name	Strength	Oral Dose Form	Number Dispensed and Frequency	Duration
E2027	25 mg	capsules	2 × 25 mg capsule QD	12 weeks
Placebo	N/A	E2027-matched capsules	2 × E2027-matched placebo capsule QD	12 weeks

N/A = not applicable, QD = once daily.

9.4.2 Identity of Investigational Product(s)

Test drug and placebo will be supplied by the sponsor in labeled containers.

9.4.2.1 Chemical Name, Structural Formula of E2027

- Test drug code: E2027
- Generic name: not applicable
- Chemical name: 7-(2-Methoxy-3,5-dimethylpyridin-4-yl)-1-[(3*S*)-tetrahydrofuran-3-yl]-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one maleate (International Union of Pure and Applied Chemistry [IUPAC])
- Molecular formula: $C_{22}H_{22}N_4O_3 \cdot C_4H_4O_4$
- Molecular weight: 506.52 (390.44, free base)

9.4.2.2 Comparator Drug

Subjects will not receive an active comparator study drug. An inactive placebo will be used, with all subjects maintaining their current standard of care.

9.4.2.3 Labeling for Study Drug

E2027 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language for each of those countries. The following information will be provided:

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

9.4.2.4 Storage Conditions

Storage and handling instructions for E2027 capsules and the placebo capsules are provided on the investigational product labels

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

9.4.4 Selection of Doses in the Study

Based on animal cognition models, a sustained increase of CSF cGMP from baseline by 150% or higher after dosing to steady state is thought to be required for clinical efficacy, which is therefore regarded as a minimum target PD effect required of the doses in this study. In the Pfizer Phase 2 monotherapy study of a PDE9 inhibitor (PF-04447943), it was estimated that it would achieve a maximal ~100% increase in CSF cGMP from baseline at steady state, but the study showed no significant efficacy in AD subjects. Thus, the level of CSF cGMP elevation above 100% required for cognitive improvement in AD or LBD patients is unknown. Therefore, in this clinical efficacy POC study, it is important to investigate the procognitive effects of a E2027 dose that results in a higher of CSF cGMP elevation from baseline at ≥150%.

In the MAD study (Study 002) in healthy subjects (aged 50 to 85), the safety, tolerability, PK, and PD effects of E2027 on CSF cGMP were investigated at 25, 50, 100, 200 and 400 mg QD × 14 days. Mean CSF cGMP % increase from baseline at trough (predose) steady state ($A_{min,ss}$) and mean E2027 PK parameters for the various doses are shown in Table 1. The dose-PD response relationship appears to saturate at 50 mg QD so higher doses do not appear to offer a higher probability of efficacy. Consequently, it is proposed that the dose in Study 201 should be 50 mg QD, at which CSF cGMP elevation from baseline was ~200% and higher than the minimum level associated with procognitive effects in animal models. In principle PK/PD modelling suggests that a lower dose of ~ 20 mg QD has mean CSF cGMP elevation from baseline of ~150% but given the variability of the CSF PD response, such a lower dose will have some overlap in its distribution of CSF PD effects with the 50 mg QD dose. This makes it less likely for differentiation of clinical efficacy from the 50 mg QD dose. Therefore, as Study 201 is the first efficacy study in the target patient population, a lower dose is not included. The dose-efficacy relationship will be evaluated later during clinical development, if the 50 mg QD dose is shown to be efficacious.

All doses investigated to date were well-tolerated with no clinically significant safety findings in vital signs, ECG intervals, or laboratory tests.

9.4.5 Selection and Timing of Dose for Each Subject

E2027 is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and treatment will continue for 12 weeks. Subjects should withhold administration of study drug in the morning of the study visit days that blood will be drawn in the clinic for PK analysis (Table 6). Subjects will be instructed to take their other concomitant medications at the usual time.

9.4.6 Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. 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 standard operating procedure (SOP).

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor, the interactive voice and web response system (IxRS) vendor, and the sponsor. 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. It is solely the investigator's responsibility in an emergency to decide if breaking the code is necessary based on clinical judgement. (revised per Amendment 02)

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study starting at the date of informed consent will be recorded. The adverse event or medical condition for which the concomitant medication or therapy was administered will be recorded.

9.4.7.1 Drug-Drug Interactions

Instructions for use of medications that may interact with E2027 are described in Section 9.4.7.2.

9.4.7.2 Prohibited and Restricted Concomitant Therapies and Drugs

Unless otherwise specified, the following medications are prohibited from a period of 14 days (or 5 half-lives, whichever is longer) before the Baseline Visit (Visit 2) until the Follow-Up Visit to avoid the risk of interaction with E2027. Subjects who start any of these medications during the study will be discontinued.

- Drugs known to be strong inhibitors of cytochrome P450 (CYP) 3A, which increase exposure of drugs that are CYP3A substrates by >5 fold, grapefruit, grapefruit juice, and grapefruit products.
- Drugs known to be moderate to strong inducers of CYP3A. Herbal preparations containing St. John's Wort is prohibited for 4 weeks before the Baseline Visit (Visit 2) until the Follow-Up Visit.
- Drugs known to cause prolongation of the QT interval, including but not limited to drugs that may cause cardiac arrhythmias. For drugs that may cause QTcF prolongation, subjects need not be excluded, if at Screening subjects are already on stable doses for at least 4 weeks and their mean QTcF on triplicate ECGs at Screening and Baseline Visit is not >450 ms (Exclusion Criterion 15).

- Drugs that are PDE inhibitors (eg, theophylline, aminophylline, sildenafil, tadalafil, vardenafil, dipyridamole, roflumilast, apremilast, inamrinone, milrinone, and enoximone)

The following medications are prohibited to avoid the risk of interference with study assessments or procedures. Subjects who start these medications during the study will be discontinued unless otherwise specified.

- Anticholinergic drugs that have CNS activity are prohibited from 4 weeks before Screening Visit until the Follow-Up Visit.
- Pimavanserin is prohibited for 12 weeks before Screening Visit until the Follow-Up Visit. (revised per Amendment 03)
- In subjects who participate in the CSF substudy only, anticoagulants (eg, heparin, heparin derivatives, non-heparin derivatives, warfarin, dabigatran) and dual antiplatelet therapy (eg, aspirin and clopidogrel together) are prohibited from Screening Visit until after the 2nd CSF collection at 9 weeks postrandomization. These subjects who start anticoagulants or dual antiplatelet therapy at any time before CSF collection at 9 weeks postrandomization will not participate in the CSF substudy.

The following restrictions apply to AChEIs (including donepezil, rivastigmine, galantamine) for treatment of DLB:

- If a subject is already receiving AChEI at Screening, then they must be on a stable dose for at least 12 weeks before Screening and remain on the same dose during the study until the Follow-Up Visit.
- If a subject is not already receiving AChEI at Screening, then these should not have been used for at least 12 weeks before Screening and AChEI should not be started during the study until the Follow-Up Visit.
- As far as it is feasible subjects who start AChEI or change their dose of AChEI during the study should undertake an Unscheduled Visit before making such changes in their AChEI medications to undertake efficacy assessments (MoCA, CIBIC-Plus, MMSE, SCOPA-Sleep, NPI, CFI, CGIC-DLB) (unless they have been conducted within past 4 weeks). This change in AChEI medication is considered a protocol deviation and the handling of efficacy data collected after the change of these medications in the efficacy analyses is described in Section 9.7.1.6.

The following restrictions apply to memantine for treatment of DLB (revised per Amendment 03):

- If a subject is already receiving memantine at Screening, they must be on a stable dose for at least 12 weeks before Screening and remain on the same dose during the study until the Follow-Up Visit.
- If a subject is not already receiving memantine at Screening, then this should not have been used at least 12 weeks before Screening and memantine should not be started during the study until the Follow-Up Visit.
- As far as it is feasible subjects who start memantine or change their dose of memantine during the study should undertake an Unscheduled Visit before making such changes in their memantine to undertake efficacy assessments (MoCA, CIBIC-Plus, MMSE, SCOPA-Sleep, NPI, CFI, CGIC-DLB) (unless they have been conducted within past

4 weeks). This change in memantine is considered a protocol deviation; the handling of efficacy data collected after the change of these medications in the efficacy analyses is described in Section 9.7.1.6.

The following restrictions apply to medications for Parkinson's disease or motor symptoms of DLB (except CNS-active anticholinergic drugs that are prohibited as above):

- If a subject is already on any of these medications at Screening, then they must be on a stable dose for at least 4 weeks before Screening and remain on the same dose during the study until the Follow-Up Visit.
- If a subject is not already on any of these medications at Screening, then these should not be started during the study until the Follow-Up Visit.
- Starting or changing the dose of these medications during the study is considered as protocol deviation and the handling of efficacy data collected after the change of these medications in the efficacy analyses is described in Section 9.7.1.6.

The following restrictions apply to medications for antipsychotic or neuroleptic drugs, Yi Gan San, hypnotics, anxiolytics or antidepressants:

- If a subject is already on any of these medications at Screening, then they must be on a stable dose for at least 4 weeks before Screening and remain on the same dose during the study until the Follow-Up Visit.
- If a subject is not already on any of these medications at Screening, then these should not be started during the study until the Follow-Up Visit.
- As far as it is feasible subjects who start or change their dose of these medications should undertake an Unscheduled Visit before making such changes in these medications to undertake efficacy assessments (MoCA, CIBIC-Plus, MMSE, SCOPA-Sleep, NPI, CFI, CGIC-DLB) (unless they have been conducted within past 4 weeks). This change in such medications is a protocol deviation and the handling of efficacy data collected after the change of these medications in the efficacy analyses is described in Section 9.7.1.6.

The following restrictions apply to other medications that the subject is taking at Screening or are started during the study:

- These medications may be permitted if they are not included in the prohibited or restricted medications list above, and are considered by the investigator and sponsor medical monitor not to compromise study assessments or subject safety.
- Permitted prior medications should be at a stable dose for at least 4 weeks before Screening and as far as possible remain on the same dose throughout the study.
- Subjects who change the dose of their permitted prior medications or who start permitted new medications during the study may continue in the study if the investigator and sponsor medical monitor consider that this will not compromise study assessments or subject safety.
- As needed (PRN) medications required for performing LP for CSF sampling are permitted in the CSF substudy.

9.4.7.3 Other Restrictions

E2027 absorbs light within the range of natural sunlight (290 - 700 nm). This possible effect of photosensitive skin reactions has not been fully evaluated in humans. In clinical studies conducted with E2027, which included subjects treated with E2027 50 mg QD for 6 weeks, there were no reported AEs of skin sensitivity due to exposure to sunlight. Until photosensitivity is evaluated, subjects are advised to avoid exposure to artificial ultraviolet light and excessive or prolonged exposure to sunlight while taking the study drug. (revised per Amendment 01)

Male subjects who are currently in the treatment period are required to practice highly effective contraception throughout the treatment period and for 98 days after study drug discontinuation if they meet both of the following criteria: (1) have not had a successful vasectomy (confirmed azoospermia); (2) have female partners of childbearing potential. (revised per Amendment 05) Male subjects meeting such criteria but who cannot practice contraception will be discontinued from study drug.

Male subjects who have already discontinued study drug at the time of Amendment 05, but for whom less than 98 days have passed since taking their final dose of study drug, are required to practice highly effective contraception until 98 days after study drug discontinuation if they meet both of the following criteria: (1) have not had a successful vasectomy (confirmed azoospermia); (2) have female partners of childbearing potential.

The following highly effective contraception methods are acceptable:

- Total abstinence (if it is their preferred and usual lifestyle)
- An intrauterine device or intrauterine hormone-releasing system (IUS)
- A contraceptive implant
- An oral contraceptive
  - Female partners of male subjects who are currently in the treatment period must be on a stable dose of the same oral contraceptive product for at least 28 days before male subject's dosing and throughout the treatment period and for 98 days after study drug discontinuation
  - Female partners of male subjects who have already discontinued study drug at the time of Amendment 05 must be on a stable dose of the same oral contraceptive product for at least 28 days before the implementation of Amendment 05 and continue until 98 days after the male subject's study drug discontinuation

No sperm donation is permitted throughout the treatment period and for 98 days after study drug discontinuation.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. Clinical research associates (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 Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their 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

After the subject has provided informed consent, screening assessments will be performed in 6 tiers as noted in Table 6. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence.

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, and ethnicity. For caregivers or informants, their age, sex, relationship to subject, residential status with the subject, and time spent per week with the subject will be collected at the Screening Visit.

9.5.1.2 Baseline/Screening Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. (revised per Amendment 03) All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions electronic case report forms (eCRFs). Medical history will include history of DLB.

Physical examinations 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, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). 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 AE eCRF.

9.5.1.2.2 OTHER SCREENING/BASELINE ASSESSMENTS

In addition, the following tests will be performed during screening (see Table 6): GDS, SFQ, HYS, safety brain MRI, DAT brain imaging and myocardial MIBG scan.

Geriatric Depression Scale (GDS)

This is a self-reported, clinician-assisted scale designed to identify symptoms of depression in the elderly. The scale consists of 15 questions that the subject is asked to answer about how they felt over the past week. Answers to 5 of the items are negatively oriented for depression (eg, Do you feel full of energy?) and 10 positively oriented (eg, Do you often feel helpless ?). One point is given for each appropriate positive or negative answer indicative of a symptom of depression, for a possible total of 15 points. Total scores of 0 to 5 are considered normal and scores of 6 to15 are considered depressed. Subjects with DLB who have a GDS score >8 are considered to have significant depressive symptoms which may contribute to cognitive deficits and are excluded.

Short Fluctuation Questionnaire (SFQ)

This scale consists of 8 questions as to whether fluctuation occurs in various domains including attention, ability to performance daily functions, orientation, verbal communication and behavior. It is scored as 1 for presence of fluctuation in each domain and 0 for absence. It has a score range of 0 to 8. Investigators should take into account the SFQ score in deciding if a subject meets one of the core criteria (fluctuating cognition) for diagnosis of DLB.

Hoehn and Yahr Scale (HYS)

This scale is used to stage (I to V) the severity of motor features in Parkinson's disease. It captures typical patterns of progressive motor impairment. It is based on the extent of anatomical distribution of the extrapyramidal features (unilateral or bilateral, limbs or limbs and trunk) and severity (mild, moderate, severe, loss of mobility). Subjects with Stage IV disease (severe disability but still able to walk or stand unassisted) or worse are excluded.

Safety Brain MRI

Safety brain MRI will be conducted at Screening to identify various exclusionary lesions and other MRI abnormalities which may indicate significant contribution to cognitive impairment from non-DLB causes (Section 9.3.2). The MRI settings will be described in the MRI manual provided by the central MRI reader, who will also review all MRI scans for eligibility.

DAT Brain Scan

In this brain scan, an intravenous radiopharmaceutical ^{123}I-ioflupane that selectively binds to the striatal dopamine transporter in the brain is administered. It is used to visualise the levels of DAT in the striatum (caudate and putamen) using single-photon emission computed tomography (SPECT) brain imaging. In subjects with Parkinsonian syndromes including DLB and Parkinson's disease, there is reduced DAT signal in the scan in the striatum (putamen and caudate). This pattern may be asymmetrical between left and right sides or there may be diffuse reduction on both sides. DAT scans will be evaluated by a central reader. Subjects who undertake DAT brain imaging are required to have abnormal (low uptake of ^{123}I-ioflupane) in the striatum as 1 of the eligibility criteria.

MIBG Myocardial Scan

In this cardiac scan, an intravenous radiopharmaceutical ^{123}I-meta-iodobenzylguanidine (MIBG) that is selectively taken up via the norepinephrine transporter into the post-ganglionic sympathetic nerve terminals in the heart is administered. Uptake into these sympathetic nerve terminals is then visualised using single-photon emission computed tomography (SPECT) imaging. In subjects with Parkinsonian syndromes including DLB and Parkinson's disease, there is reduced MIBG uptake in the heart such that the ratio of the MIBG signal in the heart to the mediastinum is reduced. MIBG cardiac scans will be evaluated by a central reader. Subjects who undertake MIBG cardiac scans are required to have abnormal (low uptake of MIBG) in the heart as one of the eligibility criteria.

For a detailed description of the sequence in which these assessments are administered at Screening or Baseline Visit, see Sections 9.1.1 and 9.1.2.

9.5.1.3 Efficacy Assessments

Efficacy assessments are summarized in the following sections. These assessments should be performed at approximately the same time of the day as were done at the Baseline Visit whenever possible (preferably in the morning). The MoCA should be the first clinical scale to be administered before any invasive procedures. It is recommended that other efficacy assessments in subjects should be performed in the following overall order: CIBIC-Plus, MMSE (after 12 weeks only) and SCOPA-Sleep. Other study assessments may be conducted in between these efficacy assessments.

For a detailed description of the sequence in which these assessments are administered during the Treatment and the Follow-Up Periods, see Sections 9.1.3 and 9.1.4.

9.5.1.3.1 MONTREAL COGNITIVE ASSESSMENT (MOCA)

The MoCA scale assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. It is reported to be useful to characterize global cognitive impairment in DLB. The total possible score is 30 points; a score of 26 or above is considered normal. The MoCA will be assessed as designated in Table 6.

9.5.1.3.2 CLINICIAN'S INTERVIEW BASED IMPRESSION OF CHANGE PLUS CAREGIVER INPUT (CIBIC-PLUS)

The CIBIC-Plus scale is designed to measure various domains that describe subject function: general, mental/cognitive state, behavior, and activities of daily living. It is a semi-structured global rating derived from a comprehensive interview with the subject and caregiver or informant by an independent rater who has no access to the source data or other psychometric test scores conducted postrandomization as part of the given protocol.

At Baseline (Visit 2), this independent rater will use a related tool, the CIBIS-Plus. This scale, which assesses disease severity on a 7-point scale from 1 = normal to 7 = extremely ill, establishes a point of reference for subsequent interviews using the CIBIC-Plus.

During the Treatment Period, the rater will administer the CIBIC-Plus separately to the subject and the caregiver or informant as designated in Table 6. At the end of each pair of interviews during each of these study visits, the rater alone will determine separately for each of the 4 domains whether the disease has improved, worsened, or remained unchanged since the evaluation at Baseline. The CIBIC-Plus scores are: 1 (marked improvement), 2 (moderate improvement), 3 (minimal improvement), 4 (no change), 5 (minimal worsening), 6 (moderate worsening) and 7 (marked worsening).

The CIBIC-Plus will also be assessed at ED and Unscheduled Visits.

9.5.1.3.3 NEUROPSYCHIATRIC INVENTORY (NPI)

The NPI scale assesses frequency and severity of 12 neuropsychiatric symptoms commonly described in dementia patients: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, nighttime behaviors and appetite/eating changes. The scale also assesses the degree of caregiver or informant distress engendered by each of the symptoms. It is rated from 0 to 144 with high scores meaning a greater neuropsychiatric disturbance. A subscore covering the domains of delusions, hallucinations, apathy, and depression (NPI-4) will also be derived.

The NPI will be assessed as designated in Table 6. The caregiver or informant will complete the NPI at these visits.

9.5.1.3.4 MINI-MENTAL STATE EXAMINATION (MMSE)

The MMSE is 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). The MMSE will be assessed as designated in Table 6.

9.5.1.3.5 COGNITIVE FLUCTUATION INVENTORY (CFI)

The CFI scale assesses cognitive fluctuation with the same format as the NPI. It evaluates fluctuation in various domains including attention, ability to performance daily functions, orientation, verbal communication and behavior. It is scored based on frequency and severity with a score range of 0 to 12. The scale also assesses the degree of caregiver or informant distress engendered by the symptoms. The CFI will be assessed as designated in Table 6.

9.5.1.3.6 SCALES FOR OUTCOME IN PARKINSON'S DISEASE-SLEEP (SCOPA-SLEEP)

The SCOPA-Sleep includes sections for evaluation of night time and daytime sleep. There are 5 questions for night time sleep: (1) trouble falling asleep, (2) awakening during the night, (3) episodes lying awake too long at night, (4) early morning waking and (5) patient's impression whether they had adequate duration of sleep at night. There are 6 questions for daytime sleep, (1) falling asleep unexpectedly during the day or evening, (2) falling asleep while sitting peacefully, (3) while watching television or reading, (4) while talking to someone, (5) trouble staying awake during the day or evening, and (6) experiencing falling asleep as a problem. The SCOPA-Sleep will be assessed as designated in Table 6. .

9.5.1.3.7 CLINICIAN GLOBAL IMPRESSION OF CHANGE IN DEMENTIA WITH LEWY BODIES (CGIC-DLB)

The CGIC-DLB provides an overall clinician-determined summary measure of change from the subject's clinical status at the Baseline Visit that takes into account all available information from the efficacy endpoints above (which include cognitive function, non-cognitive symptoms, behaviour, and the impact of the symptoms on the subject's ability to function) and safety data. It is to be performed by the investigator and is a separate efficacy assessment from the CIBIC-Plus. The CGIC-DLB will be assessed as designated in Table 6.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Collection and handling of PK, PD, and PGx samples will be detailed in the central laboratory manual to be provided to clinical sites.

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of plasma E2027 concentrations for PK analysis. Two blood samples for PK will be drawn at Week 2: at predose (within 30 minutes before dosing) and 1 to 3 hours postdose. Three blood samples for PK will be drawn at Weeks 6 and 12: at predose (within 30 minutes before dosing), 1 to 3 hours, and 4 to 8 hours postdose. Additionally, 2 blood samples for PK will be drawn at Week 9: 1 at predose (30 minutes before

dosing), and another at 1 to 4 hours postdose. At these visits, subjects or their caregivers or informants will be instructed not to take their study drug at home on the day the blood samples for PK are collected. Instead, subjects will take their study drug at the clinic after the predose blood draw; then a postdose blood draw will be performed. In addition, subjects or their caregivers or informants will be instructed to record the time of study drug administration for the 2 days before these visits when self-administered at home and this information will be collected and recorded on the eCRF.

Plasma E2027 concentrations and those of its metabolites (if appropriate) will be measured using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay methods.

In subjects who participate in the CSF substudy, CSF specimens will be collected for the determination of CSF E2027 concentrations as designated in Table 6. A predose blood sample for PK will be taken first, followed by CSF sampling. Subjects will then be administered study drug. CSF E2027 concentrations and those of its metabolites (if appropriate) will be measured using validated LC-MS/MS assay methods.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Pharmacodynamic and Other Biomarker Assessments

In subjects who participate in the CSF substudy, a CSF sample will be collected as specified in the Schedule of Procedures/Assessments (Table 6). Samples should be collected at approximately the same time in the morning, either in the fasted state (preferred) or at least 2 hours after breakfast. The CSF sample during the Treatment Period should be collected after the predose blood draw for PK analysis at the study visit after 9 weeks on study drug, followed by study drug administration. The CSF samples will be assayed for cGMP and E2027. CSF cGMP concentrations will be measured using a validated LC-MS/MS assay method. Other CSF biomarkers related to DLB or E2027 PD effects may also be assayed if appropriate.

Pharmacogenomic Assessments

PGx blood samples will be collected as specified in the Schedule of Procedures/Assessments (Table 6) where feasible and in accordance with local regulations. See the Lab Manual for a description of collection, handling, and shipping procedures of the samples. Participation in PGx assessments is voluntary and subjects must provide a separate informed consent prior to blood collection for PGx assessment.

The PGx blood samples may be used to genotype common and rare genetic variants. Data obtained from the PGx analysis will be used for research, to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The deoxyribonucleic acid (DNA) will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample may be stored for up to 15 years, based on country specific regulations to assist in any scientific research questions related to E2027 or DLB.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, and monitoring of hematology, blood chemistry, and urinalysis values; measurement of vital signs (including orthostatic changes), ECGs, the performance of physical examinations; C-SSRS and UPDRS-III as detailed in Table 6. A safety brain MRI may also be performed at Unscheduled Visits if deemed appropriate by the investigator.

9.5.1.5.1 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient 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 E2027.

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: Every sign or symptom should not be listed as a separate AE if the applicable 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, withdrawal 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. SAEs will be collected for 28 days 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 AE eCRF.

Abnormal ECG (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF 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.

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 9.5.1.5.8 for a description of the C-SSRS).

All AEs must be followed for 28 days 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.

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: fall, syncope, skin rash considered to be related to study drug, and a "yes" answer to Type 4 or 5 suicidal ideation, or a "yes" response to any suicidal behavior on the C-SSRS. It is the responsibility of the investigator to review the results of the C-SSRS and determine if any result constitutes an AE.

If a subject develops a skin rash which is considered by the investigator not to be related to study drug, then the study drug should continue. If a subject develops a skin rash that is considered by the investigator to be possibly a drug rash related to study drug, the study drug should be temporarily stopped and a PK sample should be collected. The subject should be referred to a dermatologist for evaluation. If it is concluded after dermatologist review that the skin rash is not drug rash due to study drug, study drug treatment may be resumed.

If it is concluded after dermatologist review that the skin rash is likely to be a drug rash due to study drug, then the study drug should be permanently discontinued if the rash has any of the following characteristics:

- A bullous rash regardless of severity
- A moderate to severe nonbullous rash

If it is concluded after dermatologist review that the skin rash is likely to be a drug rash due to study drug, but does not meet the above criteria for discontinuation, then study drug may be resumed after the rash has resolved.

If the rash that is considered by the investigator to be related to study drug but has resolved before the dermatologist review then the study drug should be permanently discontinued if the rash has any of the following characteristics:

- A bullous rash regardless of severity
- A moderate to severe nonbullous rash

Otherwise, the study drug may be resumed after the rash has resolved.

AEs that may signal drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. Similarly, AEs reported during the 28 days following the last dose of study drug (Follow-up Period) that might indicate physical dependency also require

a more detailed follow-up through completion of the same eCRF form. This includes AEs that fall into the categories listed below. Examples of such AEs are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. This additional follow-up of AEs that signal possible drug abuse potential, including physical dependency following discontinuation of study drug, is in line with current FDA Guidance for Industry for "Assessment for Abuse Potential for Drugs" (FDA 2017 Abuse Potential Guidelines). As neuropsychiatric symptoms are common in DLB, the investigator should exercise clinical judgement in deciding if a neuropsychiatric AE [such as those described in Appendix 3] constitute an AE of abuse potential.

Euphoria-related terms:

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Dizziness
- Thinking abnormal
- Hallucination
- Inappropriate affect

Terms indicative of impaired attention, cognition, and mood:

- Somnolence
- Mood disorders and disturbances

Dissociative/psychotic terms:

- Psychosis
- Aggression
- Confusion and disorientation
- Dissociative state

Related terms not captured elsewhere:

- Drug tolerance
- Habituation
- Substance related disorders

Physical dependence or withdraw (only for events observed within the first 4 weeks after the last dose of study drug):

- Drug withdrawal syndrome

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 adverse event 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, 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 "adverse event" (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

9.5.1.5.3 STUDY-SPECIFIC ADVERSE EVENTS

Not applicable.

9.5.1.5.4 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 5. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 6) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 5 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Coagulation[a]	INR derived from the prothrombin time, PTT
Chemistry	
Electrolytes	Chloride, 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, calcium, cholesterol, globulin, glucose, lactate dehydrogenase, phosphorus, TFT[b] (TSH, free triidothyronine, and free thyroxine), vitamin B12[b], total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

INR = international normalized ratio, PTT = partial thromboplastin time, RBC = red blood cell, TFT = thyroid function test, TSH = thyroid stimulating hormone, WBC = white blood cell.
a: In subjects who participate in the CSF substudy, a clotting screen (PTT and INR derived from the prothrombin time) will be performed.
b: Screening only.

Clinical laboratory tests during 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 eCRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the AE eCRF.

9.5.1.5.5 VITAL SIGNS, HEIGHT AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, SBP and DBP [mmHg] including orthostatic evaluations, pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), height (m), and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 6) by a validated method. Blood pressure and pulse will be measured after the subject has been resting for 10 minutes in the supine position. Blood pressure and pulse will be measured again after standing up for 2 minutes. All BP measurements should be performed on the same arm, preferably by the same person. (revised per Amendment 01)

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed prior to drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

Orthostatic (postural) hypotension will be defined as either asymptomatic orthostatic hypotension (change in blood pressure upon standing without lightheadedness) or symptomatic orthostatic hypotension (change in blood pressure upon standing accompanied by lightheadedness).

Orthostatic hypotension will be recorded based on the following criteria:

- Drop in systolic BP ≥20 mmHg, or
  Drop in diastolic BP ≥10 mmHg (revised per Amendment 01)

Occurrences of orthostatic hypotension as defined above that also meet any of the following criteria are considered clinically significant and will be reported as AEs in this study:

- Postural lightheadedness noted upon standing (ie, symptomatic orthostatic hypotension)

- Requires intervention (eg, resumption of recumbent position, IV fluids, etc.)

Postural lightheadedness upon standing if accompanied by orthostatic BP changes meeting the above criteria of orthostatic hypotension should be reported as AE of orthostatic hypotension. (revised per Amendment 01)

9.5.1.5.6 PHYSICAL EXAMINATIONS

Complete and brief physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 6). A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examinations 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. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the AE eCRF.

9.5.1.5.7 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 6). Triplicate ECG will be performed after subject has been resting in the supine position for at least 10 minutes. The mean QTcF and other ECG intervals will be determined. An ECG abnormality may meet the criteria of an AE as described in this protocol (see

Section 9.5.1.5.1) and the eCRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

9.5.1.5.8 OTHER SAFETY ASSESSMENTS

Columbia Suicide Severity Rating Scale (C-SSRS)

An assessment of suicidality using the C-SSRS will be performed as designated in the Schedule of Procedures/Assessments (Table 6).

Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS UPDRS) Part III: Motor Examination

The MDS UPDRS scale evaluates extrapyramidal features in motor function in Parkinson's disease. It contains 33 items in 18 categories: (1) speech, (2) facial expression, (3) rigidity, (4) finger tapping, (5) hand movements, (6) supinational and pronation movements of hands, (7) toe tapping, (8) leg agility, (9) arising from chair, (10) gait, (11) freezing of gait, (12) postural stability, (13) posture, (14) body bradykinesia, (15) postural tremor of hands, (16) kinetic tremor of hands, (17) rest tremor amplitude and (18) constancy of rest tremor. Each item is scored 0 to 4, giving a total score range 0 to 132. As far as is practical, the motor assessments should be made with the subject in the "on" state at each visit and at the same time relative to the subject's last dose of Parkinson's disease medication (such as L-dopa). (revised per Amendment 01)

9.5.1.6 Other Assessments

9.5.1.6.1 DEMENTIA-RELATED QUALITY OF LIFE AS ASSESSED BY THE DEMENTIA QUALITY OF LIFE MEASURE (DEMQOL; INTERVIEW OF SUBJECT) AND DEMENTIA QUALITY OF LIFE MEASURE BY PROXY (DEMQOL-PROXY; INTERVIEW OF CAREGIVER ABOUT SUBJECT)

The DEMQOL and DEMQOL-Proxy are appropriate for use in subjects with mild-moderate dementia (MMSE ≥10). The DEMQOL is a 28-item scale and DEMQOL-Proxy is a 31-item scale. Both are interview administered. There are 5 domains: daily activities, health and well-being, cognitive functioning, social relationships and self-concept. All items are given a score from 1 to 4 and summed to produce domain scores. A general quality of life item is unscored. The DEMQOL and DEMQOL-Proxy will be assessed at Baseline (Visit 2) and Day 84 (Visit 8). Should the subject progress to severe dementia during the course of the study, only the DEMQOL-Proxy should be administered.

9.5.1.6.2 GENERAL HEALTH STATUS AS ASSESSED BY THE EUROQOL- 5 DIMENSION QUESTIONNAIRE (EQ-5D; COMPLETED BY SUBJECT) AND EUROQOL- 5 DIMENSIONS QUESTIONNAIRE BY PROXY VERSION 1 (EQ-5D PROXY; CAREGIVER COMPLETION OF REPORT ABOUT SUBJECT)

The EQ-5D is a widely used general health state and health utility scale to assess the impact of any health intervention on the general quality of life of patients. The health utility values are utilized as weights to life expectancy estimates and ultimately are used in a metric known as

an incremental cost effectiveness ratio (ICERs). ICERs are used by health authorities to make key decisions that ultimately impact the relative funding of health interventions across multiple therapeutic areas based on their relative cost-effectiveness. Thus, the EQ-5D is not specifically developed for any particular disease to allow this cross-therapeutic comparison.

The scale consists of 5 specific questions (regarding mobility [walking], self-care [washing and dressing], usual activities, pain/discomfort, and anxiety/depression) and 1 overall health rating. The EQ-5D is selected in this study due to its brevity and content. The EQ-5D-5L (5 levels of responses to each of the 5 questions) will be utilized in this study as it allows for a more granular assessment of the impact of intervention.

The proxy EQ-5D version is available as EQ-5D-5L (5 levels of responses to each of the 5 questions) and will be utilized to assess the caregiver's or informant's perspective of the subject's health. The proxy EQ-5D-5L is available in 2 versions: Proxy version 1 where the caregiver or informant (the proxy) is asked to rate the patient's health-related quality of life in their (the proxy's) opinion and Proxy version 2 where the caregiver or informant (the proxy) is asked to rate how he/she (the proxy) thinks the subject would rate his/her own health-related quality of life, if the subject were able to communicate it. Only Proxy version 1 will be utilized in this particular study. The EQ-5D and EQ-5D-Proxy will be assessed at Baseline (Visit 2) and Day 84 (Visit 8).

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 study.

Table 6 Schedule of Procedures/Assessments in Study E2027-G000-201

Phase	Prerandomization		Randomization								
Period	Screening	Baseline	Treatment						Follow-Up	Early Discontinuation (ED) [d]	Unscheduled [e]
Visit [a]	1 [b]	2 [c]	3 [c] Telephone	4	5	6	7	8	9		
Day	-42 to -8	-7 to -1	1	14	28	42	63	84	112		
Weeks elapsed since randomization			0	2	4	6	9	12	16		
Assessments											
Informed consent	X										
Informed consent for CSF substudy (optional)	X										
Inclusion and exclusion criteria	X	X									
Demographics	X (Tier 1)										
Medical history	X (Tier 1)										
History of DLB	X (Tier 1)										
Prior and concomitant medications	X (Tier 1)	X	X	X	X	X	X	X	X	X	X
MMSE [f,g]	X (Tier 2)							X	X	X	X
GDS [f]	X (Tier 2)										
MoCA [f,g]	X (Tier 2)	X				X		X	X	X	X
SCOPA-Sleep [f,g]	X (Tier 2)	X				X		X	X	X	X
SFQ [f]	X (Tier 2)										
CFI [f,g]	X (Tier 2)	X				X		X	X	X	X
NPI [f,g]	X (Tier 2)	X				X		X	X	X	X
CIBIS-Plus [g]		X									

Table 6 Schedule of Procedures/Assessments in Study E2027-G000-201

Phase	Prerandomization		Randomization								
Period	Screening	Baseline	Treatment						Follow-Up	Early Discontinuation (ED) [d]	Unscheduled [e]
Visit [a]	1 [b]	2 [c]	3 [c] Telephone	4	5	6	7	8	9		
Day	-42 to -8	-7 to -1	1	14	28	42	63	84	112		
Weeks elapsed since randomization			0	2	4	6	9	12	16		
Assessments											
CIBIC-Plus [g]						X		X		X	X
CGIC-DLB						X		X		X	X
DEMQOL-Proxy		X						X			
DEMQOL		X						X			
EQ-5D		X						X			
EQ-5D Proxy		X						X			
Modified Hachinski Ischemic Scale	X (Tier 3)										
UPDRS-III	X (Tier 3)							X	X	X	X
HYS	X (Tier 3)										
C-SSRS	X (Tier 3)	X		X	X	X	X	X	X	X	X
Height	X (Tier 4)										
Weight	X (Tier 4)							X		X	X
Vital signs [h]	X (Tier 4)	X		X	X	X	X	X	X	X	X
Complete physical examination	X (Tier 4)										
Brief physical examination		X						X	X	X	X
12-lead ECG [i]	X (Tier 4)	X		X	X	X	X	X	X	X	X
Blood and urine for clinical laboratory tests [j]	X (Tier 4)	X [j]				X		X		X	X

Table 6 Schedule of Procedures/Assessments in Study E2027-G000-201

Phase	Prerandomization		Randomization								
Period	Screening	Baseline	Treatment						Follow-Up	Early Discontinuation (ED) [d]	Unscheduled [e]
Visit [a]	1 [b]	2 [c]	3 [c] Telephone	4	5	6	7	8	9		
Day	-42 to -8	-7 to -1	1	14	28	42	63	84	112		
Weeks elapsed since randomization			0	2	4	6	9	12	16		
Assessments											
Blood for vitamin B12 test	X (Tier 4)										
Blood for thyroid function tests [k]	X (Tier 4)										
Urine drug screen	X (Tier 4)	X									X
Serum pregnancy test [l]	X (Tier 4)										
Urine pregnancy test [l]		X									
Safety brain MRI [m]	X (Tier 5)										X[m]
DAT brain imaging, MIBG scan [n]	X (Tier 6)										
CSF sample by LP for PK and PD biomarkers [o]	X						X				
Plasma sample for PK [p]				X		X	X	X		X	X
PGx sample[q]		X									
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Randomization [c]		X									
Dispense study drug		X		X	X	X	X				

CFI = Cognitive Fluctuation Inventory, CGIC-DLB = Clinician Global Impression of Change - in Dementia with Lewy Bodies, CIBIC-Plus = Clinician's Interview Based Impression of Change Plus Caregiver Input, CIBIS-Plus = Clinician Interview Based Impression of Severity plus Caregiver Input, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, DAT = dopamine transporter, DEMQOL = Dementia Quality of Life, DLB = dementia with Lewy bodies, ECG = electrocardiogram, ED = early discontinuation, EQ-5D = EuroQol Five Dimensions Questionnaire, GDS = Geriatric Depression Scale, HYS = Hoehn and Yahr Scale, LP = lumbar puncture, MIBG = [(123)I]-metaiodobenzylguanidine, MMSE = Mini-Mental State Examination, MoCA = Montreal Cognitive Assessment, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PD = pharmacodynamic, PGx = pharmacogenomic, PK = pharmacokinetic, SCOPA-Sleep = Scales for Outcome in Parkinson's disease-Sleep, SFQ = Short Fluctuation Questionnaire, UPDRS-III = Unified Parkinson's Disease Rating Scale Part III.

a: A window of ±3 days will be permitted for Visit 4 to 9 (Follow-Up) inclusive.

b: The Screening Visit takes place over a period of up to 5 weeks. Subjects who complete screening assessments in less than 5 weeks may proceed to the Baseline Period. At Screening, assessments are grouped into tiers and should be performed sequentially. Subjects will need to satisfy the eligibility criteria in each tier before proceeding to the next tier. Subjects who cannot complete screening within 5 weeks should be discussed with the sponsor for extension of the Screening Period by up to 2 weeks.

c: Visit 2 is the Baseline Visit and may be conducted up to 1 week before the first dose of study drug (ie, from Day -7 to Day -1). The Baseline Visit should be at least 2 weeks after the day of Screening Visit Tier 2 assessments. After completion of study assessments subjects who are eligible will be randomized to placebo or E2027. They will be dispensed with study drug before leaving clinic at Visit 2. Visit 3 (Day 1) will be conducted by telephone. On Day 1 the subject will start taking study drug in the morning at home. The site study staff will telephone the subject/caregiver to check that the subject has taken study drug and to elicit any AEs. Subjects who develop acute illnesses which make it inappropriate to start taking study drug may have their Baseline Period extended by 1 week after discussion with the sponsor medical monitor.

d: Subjects who discontinue study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their final dose of study drug. In addition, subjects who prematurely discontinue study drug are expected to continue in the study for the originally scheduled visits, starting with next such visit that is >7 days after the ED Visit. Subjects who prematurely discontinue the study should attend at least 1 originally scheduled visit after the ED Visit.

e: Unscheduled visits may be conducted at any time as clinically indicated in the judgment of the investigator or as specified in the protocol. Not all assessments indicated under Unscheduled Visits need to be conducted – actual assessments needed will be determined by the investigator or as specified in the protocol and will be based on the specific visit.

f: At Screening, Tier 2 assessments in subjects should be performed in the following order: MMSE and GDS first; then MoCA and SCOPA-Sleep. The caregivers or informants should complete the SFQ, CFI and NPI. Subjects who do not meet eligibility criteria on MMSE or GDS should be screen failed and the other assessments do not need to be performed. The caregiver or informant must attend in person with the subject. The above assessments should be completed before more invasive procedures (eg, physical examination, ECG, blood draws). Assessments at all other tiers are not required to be performed in any prespecified order.

g: At Visits 2, 6, 8, ED Visit and FU Visit, study assessments should be conducted at approximately the same time of the day whenever possible (preferably in the morning). The MoCA should be administered first. It is recommended that after the MoCA the following efficacy assessments in subjects should be performed in the following overall order (other study assessments may be conducted in between these efficacy assessments): CIBIS/CIBIC-Plus, MMSE (Visit 8 only) and SCOPA-Sleep. The caregiver or informant will also complete the CIBIS/C-Plus, NPI and CFI. The caregiver or informant must attend in person with the subject. The CIBIS-Plus and CIBIC-Plus should be performed by an independent rater from other scales. As far as possible efficacy assessments should be completed before more invasive procedures (eg, physical examination, ECG, blood draws) unless otherwise specified. At Visits 6, 8 and ED Visit the MoCA should be the first clinical scale to be administered postdose and before the first postdose PK sample. At Visits 6, 8 and ED Visit the investigator should complete the CGIC-DLB after reviewing all the subject's efficacy endpoints.

h: Single measurements of vital signs will be performed after subject has been resting supine for at least 10 minutes. Vital signs include temperature, respiratory rate, supine blood pressure and pulse. Blood pressure and pulse will be measured again after standing up for 2 min. At Week 2 (Visit 4), Week 6 (Visit 6) and Week 12 (Visit 8) (or ED Visit) vital signs will be taken at 1 – 3 hours postdose, before PK sampling. At Week 9 (Visit 7) vital signs will be taken at 1 – 4 hours postdose, before PK sampling. (revised per Amendment 01)

i: Triplicate ECG will be performed after subject has been resting supine for at least 10 min. The mean QTcF and other ECG intervals will be determined.

j: Clinical laboratory tests consist of hematology (complete blood count), clinical chemistry and urinalysis. In subjects who participate in the CSF substudy, clotting screen (PT, APTT, and INR) will also be performed only at the Screening Visit after eligibility has been established and consent for CSF has been given, but before the LP.

k: Thyroid function tests include thyroid stimulating hormone, free triidothyronine, and free thyroxine.

l: Female subjects who are <60 years of age and not surgically sterilized.

m: Safety MRI of the brain will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images at screening. MRI of the brain will be read by an approved central reader. Safety MRI of the brain may be performed at Unscheduled Visits if deemed appropriate by the investigator, but is not required for all Unscheduled Visits. Subjects who are rescreened do not need to have a new MRI at rescreening if there was an MRI within 90 days before rescreening that did not have exclusionary characteristics.

n: DAT brain imaging scan or myocardial MIBG scan will be performed by the local hospital radiology department in accordance with local procedures and must be performed at least 7 full days prior to Baseline. The rules regarding when DAT brain imaging or MIBG scan will be performed are specified in Inclusion Criterion 2.

o: CSF will be collected by LP in subjects who participate in the CSF substudy. During Screening CSF may be collected at any time after completion of screening procedures and a subject is deemed eligible at least 1 week before Visit 2; if necessary in these subjects the Screening Period may be extended by 1 week after discussion with the sponsor medical monitor. CSF will be collected again at Visit 7. CSF will be collected in the morning at approximately the same time, either fasted (preferred) or at least 2 h after breakfast. The timing of the Screening CSF collection needs to be scheduled carefully such that subsequent collection (at Visit 7) can be performed at a similar time of day (±2 hours) for each individual subject. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation. If the LP and cognitive tests are performed on the same day, the LP must be performed after the cognitive tests are completed. At Visit 7, a predose blood sample for PK will be taken first, followed by LP. Subjects will then be dosed with study drug and a PK sample will be collected at 1 – 4 hours postdose. If Visit 7 occurs after an ED Visit, blood PK samples and CSF will not be collected.

p: The day before the visits at which PK sampling will be done, the site study team will phone the subject and caregiver/informant to remind the subject not to take the study drug in the morning of the visit on the next day. In the morning of the day of the visit, the subjects should take breakfast at home as normal if applicable. Thereafter a predose PK sample will be taken in clinic. Study drug will be administered and 1 postdose PK sample will be taken: 1 - 3 hours postdose at Week 2 (Visit 4). Study drug will be administered and 2 postdose PK samples will be taken: 1 - 3 hours postdose and 4 - 8 hours postdose at Week 6 (Visit 6) and Week 12 (Visit 8) (or ED Visit). At Week 6 (Visit 6) and Week 12 (Visit 8) (or ED Visit) study drug will be administered before efficacy assessments are performed. Study drug will be administered and 1 postdose PK sample will be taken 1 - 4 hours postdose at Week 9 (Visit 7). In subjects who participate in the CSF substudy a predose PK sample will be collected at Week 9 (Visit 7), followed by CSF collection. The subject will then be dosed with study drug and a PK sample will be collected at 1 - 4 h postdose. In addition, subjects or their caregivers/ informants will need to record the time of dosing of study drug at home for 2 days before these visits. If these visits take place after the ED Visit, blood PK samples will not be collected.

q: PGx participation is voluntary. For subjects who have provided separate informed consent to participate in the PGx assessment, a blood sample for genomic DNA will be collected at the Baseline Visit. If it cannot be collected at the designated time point, it may be collected at a time point after baseline.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 6 for the timings of the procedures and assessments to be performed during the study. See Sections 9.1 and 9.5 for a full description of the procedures and assessments, respectively, to be performed during this study.

Table 7 presents the number of blood and CSF samples, and the estimated 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. Actual specimen volumes may vary based on local regulations.

Table 7 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Number of Time Points × Volume per Collection (mL)			Total Volume (mL)
		Screening Visit	Baseline Visit (predose)	Treatment and Follow-Up Periods	
Blood					
Chemistry (revised per Amendment 01)	4	1 × 2.5	1 × 2.5	2 × 2.5	10.0
Vitamin B12	1	1 × 1.3	None	None	1.3
TSH, T4, T3, βHCG	1	1 × 2.5	None	None	2.5
Hematology (revised per Amendment 01)	4	1 × 2.0	1 × 2.0	2 × 2.0	8.0
INR, prothrombin time, PTT (revised per Amendment 01)	1	1 × 2.0			2.0
PK	10	None	None	10 × 6	60
PGx	1	--	1 × 6	None	6
Total blood volume to be collected (revised per Amendment 01)		**10.3**	**10.5**	**69**	**89.8**
CSF					
PK and PD	2	1 × 6	--	1 × 6	12
Total CSF volume to be collected		**6**	--	**6**	**12**

βHCG = beta-human chorionic gonadotropin, CSF = cerebrospinal fluid, INR = international normalized ratio, PGx = pharmacogenomics, PK = pharmacokinetic(s), PTT = partial thromboplastin time, TSH = thyroid stimulating hormone, T3 = triiodothyronine, T4 = thyroxine.
Note: Actual volumes may be less, based on regional differences in Central Laboratories.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of LBD and other forms of dementia. Further discussion of the selection of the efficacy endpoints is provided in Section 9.2.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations, neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and UPDRS-III. Safety MRI of the brain may be performed at Unscheduled Visits if deemed appropriate by the investigator.

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 SERIOUS ADVERSE EVENTS, 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 the date the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected through the last visit after the last dose of study drug. 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 a female subject in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any pregnancy in a female partner of a male subject in which the estimated date of conception is either before the last visit or within 98 days of last study treatment (revised per Amendment 05), 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 be withdrawn from the study

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 AE 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 AE eCRF.

9.5.4.3.2 REPORTING OF STUDY-SPECIFIC EVENTS

Not applicable.

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

AEs 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 Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects (revised per Amendments 02 and 05)

There are no safety signals identified in clinical studies conducted to date to warrant specific discontinuation criteria for individual subjects based on safety data. Most adverse events on E2027 were mild to moderate and there were no subjects who discontinued treatment due to adverse events. Therefore the investigator should exercise clinical judgement to decide if a

subject should be discontinued, except for specific situations described below. (revised per Amendment 02)

Skin Rash

As already described in Section 9.5.1.5.1, in subjects with skin rash, if it is concluded after dermatologist review that the skin rash is likely to be a drug rash due to study drug, then the study drug should be permanently discontinued if the rash has any of the following characteristics (revised per Amendment 02):

- A bullous rash regardless of severity (revised per Amendment 02)
- A moderate to severe nonbullous rash (revised per Amendment 02)

As already described in Section 9.5.1.5.1, in subjects with skin rash, if the rash is considered by the investigator to be related to study drug but has resolved before the dermatologist review then the study drug should be permanently discontinued if the rash has any of the following characteristics:

- A bullous rash regardless of severity (revised per Amendment 02)
- A moderate to severe nonbullous rash (revised per Amendment 02)

Prolongation of QTcF Interval on ECG

Subjects who have mean QTcF on triplicate ECG >500 ms should be discontinued. (revised per Amendment 02)

Use of Prohibited Medications

As per Section 9.4.7.2, subjects who start treatment with any of these medications during the study will be discontinued due to the risk of PK or PD interactions (revised per Amendment 02):

- Drugs known to be strong inhibitors of cytochrome P450 (CYP) 3A, which increase exposure of drugs that are CYP3A substrates by >5 fold, grapefruit, grapefruit juice, and grapefruit products. (revised per Amendment 02)
- Drugs known to be moderate to strong inducers of CYP3A. (revised per Amendment 02)
- Drugs known to cause prolongation of the QT interval, including but not limited to drugs that may cause cardiac arrhythmias. (revised per Amendment 02)
- Drugs that are PDE inhibitors (eg, theophylline, aminophylline, sildenafil, tadalafil, vardenafil, dipyridamole, roflumilast, apremilast, inamrinone, milrinone, and enoximone) (revised per Amendment 02)

As per Section 9.4.7.2, subjects who start treatment with any of these medications during the study will be discontinued due to interference with efficacy assessments or safety (revised per Amendment 02):

- Anticholinergic drugs that have CNS activity. (revised per Amendment 02)

- Pimavanserin. (revised per Amendment03)
- In subjects who participate in the CSF substudy only, if they start anticoagulants (eg, heparin, heparin derivatives, non-heparin derivatives, warfarin, dabigatran) or dual antiplatelet therapy (eg, aspirin and clopidogrel together) before their 2nd CSF collection at 9 weeks postrandomization, they will be discontinued from the CSF substudy. (revised per Amendment 02)

Decline to Loss of Capacity to Consent

- As per Section 5.3, in countries where local laws/regulations do not permit subjects lacking capacity to consent to participate in this study, then subjects who have declined to the point of lacking capacity to consent during the study will be discontinued. (revised per Amendment 02)

Contraception Requirement in Male Subjects

Male subjects who are in the treatment period and who meet the criteria that requires them and their female partners to practice contraception as specified in Section 9.4.7.3, but who cannot comply or are unwilling to do so, will be discontinued. (revised per Amendment 05)

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 6).

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 discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, 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

AEs 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/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, SOPs, 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.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding and a snapshot of the

database is obtained and released for unblinding. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

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 SAP, which will be finalized before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINTS

- Change from baseline in the MoCA total score at 12 weeks of treatment
- CIBIC-Plus scale at 12 weeks of treatment

9.7.1.1.2 SECONDARY ENDPOINTS

(Order of secondary endpoints revised per Amendment 05)

- CGIC-DLB at 12 weeks of treatment
- Change from baseline at 12 weeks of treatment in the following endpoints:
    - CFI score
    - MMSE total score
    - NPI total score, subscores and caregiver distress score
- Safety and tolerability of E2027 as measured by (revised per Amendment 02):
    - Incidence of adverse events including severe AEs, serious AEs, AEs resulting in discontinuation (revised per Amendment 02)
    - Incidence of orthostatic hypotension and orthostatic tachycardia (revised per Amendment 02)
    - Incidence of markedly abnormal laboratory values and shifts from baseline of laboratory values (revised per Amendment 02)
    - Incidence of abnormal ECG parameters and abnormal ECG findings (revised per Amendment 02)
    - Incidence of suicidality based on C-SSRS (revised per Amendment 02)
    - Changes from baseline in the total score of UPDRS-III (revised per Amendment 02)

9.7.1.1.3 EXPLORATORY ENDPOINTS

- Change from baseline at 12 weeks of treatment in the following endpoints:
    - SCOPA-Sleep total score and subscores
- Change from baseline at 12 weeks of treatment in the following endpoints:

- Each of the 5 domain scores of the DEMQOL and DEMQOL-Proxy
- EQ-5D utility score and EQ-5D health status rating

- Percentage change from baseline in CSF cGMP concentration after 9 weeks of treatment

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 postrandomization 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 postrandomization coprimary efficacy measurement
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the Full Analysis Set who sufficiently complied with the protocol. It may include subjects who complete certain pre-specified minimal exposure to the treatment and have no major protocol violations such as wrong diagnosis, error in treatment assignment, use of inhibited medication and poor compliance. The precise reasons for excluding subjects from the PPS will be fully defined and documented before database lock.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable plasma E2027 concentration with a documented dosing history
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter
- The PK/PD Analysis Set is a group of subjects with at least 1 quantifiable plasma E2027 concentration, except for placebo subjects, and at least 1 PD measurement with a documented dosing history.

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.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued 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) eCRF. The number (percent) will be presented by treatment group and total for all subjects.

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 Early Discontinuation from Study Drug eCRF. The number (percent) will be presented by treatment group and total for all subjects. Subjects who

discontinued study treatment but were followed up for efficacy assessments after treatment discontinuation will also be summarized.

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 total score; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, treatment with AChEIs (no or yes), and treatment with memantine (no or yes). (revised per Amendment 03)

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 4-week Follow-Up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The significance level for all efficacy endpoint analyses is 0.05 (2-sided), unless otherwise stated, with no adjustments for multiplicity. The efficacy analyses will be performed on the FAS except per protocol analysis will be performed on the PPS.

Baseline for the primary and secondary efficacy endpoints is defined as the last pretreatment assessment. An additional baseline, based on the mean of all prerandomization values at the Screening and Baseline assessment, will be explored due to assess potential prerandomization variability.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

E2027 is planned for use as a symptomatic treatment in subjects with DLB. The treatment effect of E2027 may be confounded by the use of rescue medications during the study. For the purposes of statistical analysis, rescue medications are defined as medications for treatment of symptoms of DLB that are prohibited or restricted (as specified in Section 9.4.7.2) and they are not used in accordance with the rules in Section 9.4.7.2.

This confounding may mask the true treatment effect of E2027 in treating subjects with DLB. The treatment effect of interest will be the efficacy as measured by coprimary endpoints that

would be observed at 12 weeks without initiation or dose change of any prohibited or restricted medications as mentioned above regardless of whether or when the assigned treatment was discontinued due to adverse event, lack of efficacy or any other events related to treatment or study outcome. The target population (DLB subjects) is defined by inclusion/exclusion criteria.

There are 2 coprimary efficacy endpoints, change from baseline in the MoCA total score at 12 weeks and CIBIC-Plus scale at 12 weeks. Overall, there are 2 null hypotheses (H_0) to be tested in the primary analysis:

- H_{01}: There is no difference in the mean change from baseline in the MoCA total score at 12 weeks between E2027 and placebo.
- H_{02}: The proportional odds ratio based on CIBIC-Plus scale at 12 weeks between E2027 and placebo is equal to 1.

The corresponding 2 alternative hypotheses are that there is a difference in the mean change from baseline in MoCA total score at 12 weeks in this coprimary endpoint between E2027 and placebo and the proportional odds ratio based on CIBIC-Plus scale at 12 weeks between E2027 and placebo is not equal to 1.

The study will be considered positive if statistically significant improvement is observed in both coprimary endpoints in the E2027 treatment group.

The change from baseline of MoCA total score for E2027 compared to placebo will be analysed using the approach proposed by Mehrotra, et al. (2017) with slight modification based on reasons for missing. The following is a list of the missing reasons and their missing mechanisms:

- Data not observed because of dropouts due to AEs, lack of efficacy or any other events related to treatment or study outcome will be considered as missing not at random (MNAR).
- The effect had rescue medication not been made available to subjects prior to Week 12 is not observable for subjects who initiated prohibited or restricted rescue medication. For these subjects, the data collected after initiation of prohibited rescue medication are assumed to contain no treatment effect in the E2027 treatment group. Technically, response data collected after initiation of prohibited rescue medication will be treated as MNAR such that response data as MNAR in the E2027 treatment group would be imputed by the mean response in the placebo treatment group as described by the imputation method below.
- Data not observed because of dropouts due to intercurrent events definitely not related to treatment or outcome (eg, withdraw consent due to logistical problems) will be considered as missing at random (MAR). All events will be classified unambiguously in the statistical analysis plan.

The mean of missing endpoint values in the E2027 treatment group considered as MAR would be imputed using the mean of missing endpoint values of completers in the E2027 treatment

group and the mean of missing endpoint values in E2027 treatment group considered as MNAR will be imputed by the mean of the overall endpoint distribution under placebo based on the above missing reasons and the corresponding missing mechanisms. The mean of the overall endpoint distribution under placebo will be obtained using mixed effects model of repeated measures (MMRM) within the placebo group assuming MAR. Test statistics and the *P*-value will be obtained as described by Mehrotra, et al. (2017).

The sensitivity analysis for MoCA will be a tipping point analysis based on control-based mean imputation proposed by Mehrotra, et al. (2017) in the same article, which is an increasingly more conservative means such that the *P*-value is equal to the pre-specified alpha (0.025 [1-sided]). Drug benefit is interpreted as convincing if the tipping point is worse than the mean placebo dropouts. Additional sensitivity analysis for different classification of missing mechanism (ie, all missing data will be considered as MNAR regardless of reason of dropouts), will be provided.

In order to generate inputs for proposed primary and sensitivity analyses, a MMRM will be used for the E2027 group completers, placebo group completers, and all placebo group subjects. The model will be adjusted for baseline MoCA, visit (Weeks 6 and 12), randomization stratification variable (receiving AChEI or not; geographical region [North America, Europe, Japan]), and baseline MoCA × visit as fixed effects. An unstructured covariance matrix will be used to model the covariance of within subject effect. The values of baseline MoCA will be adjusted using the overall baseline mean of all study subjects in computing LS-means.

The primary analysis of CIBIC-Plus scale at 12 weeks will be based on control-based pattern imputation at subject level (Yuan 2014). The CIBIC-Plus scale at 12 weeks will be imputed as an ordinal response variable. The same missing reasons and corresponding missing mechanism as in the analysis of change from baseline in MoCA total score will be used in this analysis. Only the missing ordinal responses in E2027 treatment group considered as MNAR will be imputed by ordinal responses observed in the placebo group using a pattern-mixture model approach under MNAR assumption. Other missing ordinal responses will be imputed assuming MAR. The CIBIC-Plus scale at 12 weeks (observed or imputed) will be analysed using proportional odds model, a special case of generalized linear mixed models (GLMM), in multiply imputed data sets. The results obtained from all multiply imputed data sets will be combined for overall inference using Rubin's rules. The GLMM model will include treatment, randomization stratification variables (receiving AChEI or not; geographical region [North America, Europe, Japan]) as fixed effects. The model will be fitted using GLMM with a multinomial distribution and a cumulative logit link function. The proportional odds ratio estimate between E2027 and placebo, the corresponding 95% CI, and *P*-values will be presented.

The sensitivity analysis for CIBIC-Plus scale will be a tipping point analysis based on multiple imputation at subject level using pattern mixture model approach (Yuan, 2014), which is based on an increasingly more conservative shift parameter (based on cumulative logit function values for CIBIC-Plus scale) such that the *P*-value is equal to the pre-specified alpha (0.05 [2-sided]). Additional sensitivity analysis for different classification of missing

mechanism (ie, all missing data will be considered as MNAR regardless of reason of dropouts), will be provided.

If the proportional odds assumption is contradicted by the observed data in either entire population or any stratum, the GLMM method will be replaced by the non-parametric van Elteren test in both primary analysis and sensitivity analysis. The CIBIC-Plus scale at 12 weeks will be analysed using van Elteren test adjusting 2 randomization stratification variables (receiving AChEI or not; geographical region [North America, Europe, Japan]). The null hypothesis corresponding to the van Elteren test is that there is no difference in the location of distribution of CIBIC-Plus scale at 12 weeks between E2027 and placebo. The corresponding alternative hypothesis is that there is a difference in the location of distribution of CIBIC-Plus scale at 12 weeks between E2027 and placebo.

The potential effect of baseline MMSE on the primary result will be evaluated as an additional covariate in the primary model as appropriate. Subgroup (eg, region, age group, baseline AChEI status, baseline MMSE group, and baseline memantine status) analyses will be performed as appropriate. (revised per Amendment 03)

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The CGIC-DLB scale will be analysed as ordinal response data in a manner similar to the primary analysis of coprimary endpoint based on CIBIC-Plus. Other secondary endpoints are continuous variables and will be analyzed in a manner similar to the primary analysis of coprimary endpoint based on MoCA.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

The sleep endpoint (SCOPA-Sleep total score and subscores) will be analyzed in a manner similar to the coprimary endpoint based on MoCA.

If data permit, the relationship between E2027 PD effects on CSF cGMP (and other biomarkers) and various efficacy endpoints will be explored using correlation analysis and linear models will be fitted to further characterize the relationship between the changes in efficacy endpoints and the changes in E2027 PD variables as appropriate.

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 plasma E2027 concentration listings and for summaries of CSF E2027 concentrations by day.

A population PK approach will be used to characterize plasma E2027 PK. For this approach, PK data from this study will be pooled with existing data from Phase 1 studies. The effect of covariates on plasma E2027 PK, such as baseline characteristics/demographics, will be evaluated where feasible. Derived plasma E2027 exposure parameters, such as steady state area under the concentration time curve (AUC_{ss}) or average steady state concentration ($C_{ss,av}$)

will be calculated from the final PK model using the individual posterior estimates of the PK parameters and dosing history.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Pharmacodynamic Analyses

The PD Analysis Set will be used for the summaries and analyses of CSF PD biomarkers. The percentage change from baseline in CSF cGMP and any other PD biomarkers after at least 9 weeks of treatment with study drug postrandomization will be analyzed and presented graphically.

Pharmacodynamic/Pharmacokinetic Analyses

Data combining Phase 1 studies permitting, a population PK/PD approach will be used to characterize the relationship between plasma and/or CSF E2027 exposures and CSF PD biomarker levels. For this approach, data from this study will be pooled with relevant data from Phase 1 studies. The relationship between plasma and CSF E2027 exposure and the change from baseline of various efficacy endpoints will be explored graphically, as will the relationship between changes in CSF PD biomarkers and the change from baseline of various efficacy endpoints. Any emergent relationships will be explored through population PK/PD modeling.

The PK and PK/PD analyses will be detailed in a separate analysis plan and the results will be provided in a stand-alone report.

Pharmacogenomic Analyses

Pharmacogenomic analyses may be performed and reported separately. Details of these analyses, if appropriate, will be described in a separate analysis plan.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality (C-SSRS), UPDRS-III, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements (including orthostatic changes) will be summarized by treatment group.

9.7.1.8.1 EXTENT OF EXPOSURE

Extent of exposure will be summarized by categories of cumulative weeks as well as by categories of duration of exposure. The number and percentage of subjects for each exposure category will be presented by treatment group. Duration of exposure is the number of days between the date the subject received the first dose of study drug and the date the subject received the last dose of study drug and will be summarized using descriptive statistics for continuous variable by treatment group. Overall exposure (number of subject-weeks) is

defined as summation over all subjects' exposure durations and will be summarized 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 19.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges on or after start of study treatment or within 28 days following the last dose of study drug, having been absent at pretreatment (Baseline) or
- Reemerges on or after start of study treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity on or after start of study 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.

The number (percentage) of subjects with treatment-related TEAEs, treatment-emergent serious adverse events (SAEs) and TEAEs leading to discontinuation from study drug will be also summarized by SOC and PT. Subject data listing for each above type of AEs and AEs leading to death will also be provided.

AEs will be summarized by the following subgroups: region, treatment with AChEIs (no or yes), and treatment with memantine (no or yes). (revised per Amendment 03)

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate.

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 2 (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

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. ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) will be presented by visit and treatment group using frequency count. The number (percentage) of subjects with post-baseline abnormal ECG result in QTcF will be summarized by treatment group.

9.7.1.8.6 OTHER SAFETY ANALYSES

Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS responses will be mapped to C-CASA (Columbia- classification algorithm of suicide assessment). The incidence of suicidal ideation or suicidal behavior will be summarized by treatment group. Continuous variables will be summarized by descriptive statistics; number of subjects, mean, standard deviation, median, minimum, and maximum and categorical variables by number (percentage) of subjects.

UPDRS-III (Unified Parkinson's Disease Rating Scale Part III: Motor Examination)

Changes from baseline in the total score of UPDRS-III will be summarized using descriptive statistics for continuous variable by visit and treatment group.

9.7.1.9 Other Analyses

The quality of life endpoints (DEMQOL and DEMQOL-Proxy domain scores, and the EQ-5D and EQ-5D Proxy scores) after 12 weeks of treatment and the percentage change from baseline in CSF cGMP concentrations after 9 weeks of treatment will be analysed using ANCOVA or rank-based ANCOVA as appropriate. The ANCOVA model will include baseline as a covariate, with treatment group and randomization stratification variables as factors.

9.7.2 Determination of Sample Size

The MoCA scale was assessed in DLB subjects and reported in Biundo et al. (2016). The observed mean change from baseline in the MoCA total score at 1 year in this report is -1.04 points and the corresponding standard deviation (SD) is 1.32 points. An estimation of the mean change from baseline in the MoCA total score at 3 months is approximately -0.26 points using linear interpolation. It is assumed that E2027 would improve the MoCA total score as compared with baseline and achieve a mean treatment difference of approximately 0.6 points between E2027 and placebo at 12 weeks. The SD of change from baseline in the MoCA total score at 3 months is expected to be smaller than that at 1 year. A conservative estimate of the SD of change from baseline in the MoCA total score is 1.3 points at 12 weeks.

In a 12-week donepezil monotherapy study in subjects with DLB (E2020-J081-431), the estimated proportional odds ratio based CIBIC-Plus scale for donepezil 10 mg relative to placebo was 6.14. It is assumed that E2027 would achieve a proportional odds ratio of 2.607 relative to placebo (ie, 42% of the effect size observed in the above donepezil study).

With 80 subjects completing per arm (for 91 randomized subjects per arm, assuming a 12% dropout rate), this study will have approximately 80% power to detect the above effect sizes (ie, mean treatment difference of approximately 0.6 points based MoCA total score and proportional odds ratio of 2.607 based on CIBIC-Plus scale for E2027 relative to placebo) in both coprimary endpoints simultaneously. Therefore, the total sample size of 182 randomized subjects is planned, assuming a 12% dropouts rate.

Participation in the CSF substudy is voluntary. It is estimated that approximately 30% of subjects will participate in the CSF substudy. If the dropout rate in the CSF substudy is 12%, 20%, or 50%, then the number of subjects having final CSF assessment would be approximately 48, 44, or 27, respectively. The estimated standard deviation of percent change from baseline of cGMP concentrations after 9 weeks of treatment from pooled subjects in the CSF substudy is approximately 130%. The width of the 95% CI of treatment between E2027 and placebo for the 3 different sample sizes above would be approximately 74%, 77%, or 96%, respectively. Since mean percent change from baseline of cGMP concentrations after 9 weeks of treatment in the E2027 and placebo groups are expected to be approximately 200% and 5%, respectively, the sample size of the CSF substudy would be adequate to detect the mean difference of percent change from baseline in cGMP concentrations after 9 weeks of treatment between the E2027 and placebo groups.

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. (revised per Amendment 03)

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the study is safe to proceed unchanged or to provide recommendations to the

sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

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.

10 REFERENCE LIST

Aarsland D, Ballard C, Walker Z, Bostrom F, Alves G, Kossakowski K, et al. Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. Lancet Neurol. 2009 Jul;8(7):613-8.

Aarsland D, Litvan I, Salmon D, Galasko D, Wentzel-Larsen T, Larsen JP. Performance on the dementia rating scale in Parkinson's disease with dementia and dementia with Lewy bodies: comparison with progressive supranuclear palsy and Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2003;74:1215-1220.

Biundo R, Wies L, Bostantjopoulou S, Stefanova E, Falup-Percurariu C, Kramberger MG, Geurtsen GJ, Antonini A, Weintraub D, Aarsland D. MMSE and MoCA in Parkinson's disease and dementia with Lewy bodies: a multicenter 1-year follow-up study. J Neural Transm. 2016;123:431-438.

Boddy F, Rowan EN, Lett D, O'Brien JT, McKeith IG, Burn DJ. Subjectively reported sleep quality and excessive daytime somnolence in Parkinson's disease with and without dementia, dementia with Lewy Bodies and Alzheimer's disease. Int J Geriatr Psychiatry. 2007;22: 529–535.

Burn D, Emre M, McKeith I, De Deyn PP, Aarsland D, Hsu C, et al. Effects of rivastigmine in patients with and without visual hallucinations in dementia associated with Parkinson's disease. Movement Disorders. 2006;21(11):1899–1907

Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet. 2014;383:533–40.

Domek-Łopacińska K, Strosznajder JB. Cyclic GMP metabolism and its role in brain physiology. J Physiol Pharmacol. 2005 Mar;56 Suppl 2:15-34.

Donaghy P, Thomas AJ, O'Brien JT. Amyloid PET Imaging in Lewy body disorders. Am J Geriatr Psychiatry. 2015;23(1):23-37.

Dubois B, Tolosa E, Katzenschlager R, Emre M, Lees AJ, Schumann G, et al. Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study. Movement Disorders. 2012;27(10):1230-1238.

Grove RA, Harrington CM, Mahler A, Beresford I, Maruff P, Lowy, MT et al. A Randomized, Double-Blind, Placebo-Controlled, 16-Week Study of the H3 Receptor Antagonist, GSK239512 as a Monotherapy in Subjects with Mild-to-Moderate Alzheimer's Disease. Current Alzheimer Research. 2014; 11, 47-58.

Ikeda M, Mori E, Matsuo K, Nakagawa M, Kosaka K. Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled, confirmatory phase III trial. Alzheimer's Research & Therapy. 2015;7:4.

Li Z, Yu Z, Zhang J, Wang J, Sun C, Wang P, Zhang J. Impact of rivastigmine on cognitive dysfunction and falling in Parkinson's disease patients. Eur Neurol. 2015;74:86-91.

Matsunaga S, Kishi T, Yasue I, Iwata N. Cholinesterase Inhibitors for Lewy Body Disorders: A Meta-Analysis. International Journal of Neuropsychopharmacology. 2015;1‑15.

McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, Anand R, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study Lancet. 2000;356:2031–36.

McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017;89:88-100

Mehrotra DV, Liu F, and Permutt T. Missing Data in Clinical Trials: Control-Based Mean Imputation and Sensitivity Analysis. Pharmaceutical Statistics. 2017; 16(5):378–92

Mori E, Ikeda M, MD, Kosaka K. Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial. Ann Neurol. 2012;72:41–52.

National Institute for Health and Care Excellence (NICE). NICE guideline [NG97]. Dementia: Assessment, Management and Support for People Living with Dementia and Their Carers. June 2018. Available from: https://www.nice.org.uk/guidance/ng97

Noe E, Marder K, Bell KL, Jacobs DM, Manly JJ, Stern Y. Comparison of dementia with Lewy bodies to Alzheimer's disease and Parkinson's disease with dementia. Movement Disorders. 2004; 19(1):60-7.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry. Assessment of Abuse Potential of Drugs. January 2017.

Walker Z, Possin KL, Boeve BF, Aarsland D. Lewy body dementias. Lancet. 2015;386,1683-1697.

Yuan Y. Sensitivity Analysis in Multiple Imputation for Missing Data. SAS Global Forum 2014 Proceedings. Paper SAS270-2014.

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 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/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 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, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, 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
- eCRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source
- Electronic Clinical Outcome Assessment (e-COA) by self-reported measures

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 CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

Efficacy and safety assessments are evaluated based on the data entered into e-COA. The applicable data are input directly by each subject from the viewpoint of his/her health condition without the interpretation of the investigator.

11.5 Identification of Source Data

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

For the following items, the data recorded directly on the CRF are to be considered source data:

- reasons for discontinuation of study treatment

- comments and other information on AEs [eg, severity, relationship to study drug, outcome
- reasons for dose modification
- indication for prior/concomitant medication
- sampling times for drug concentrations
- sampling times for clinical laboratory tests

The data collected by e-COA are also considered source data.

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 CRFs, 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 SOPs 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) or, when approval is given by the sponsor, will destroy supplies and containers at the site.

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 Clinical Trial Agreement 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 Clinical Trial Agreement 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 Clinical Trial Agreement 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 Diagnostic Criteria for Probable Dementia With Lewy Bodies (DLB)

The diagnostic criteria for probable dementia with Lewy bodies (DLB) require:

- Progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions or with usual daily activities.
- Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progress.
- Deficits on tests of attention, executive function and visuospatial ability may be prominent and occur early.
- At least 2 core clinical features, or 1 core clinical feature and at least 1 indicative biomarker.

The core clinical features are:

- Fluctuating cognition with pronounced variations in attention and alertness.
- Recurrent visual hallucinations that are typically well formed and detailed.
- REM sleep behavior disorder which may precede cognitive decline.
- One or more spontaneous cardinal features of Parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor or rigidity.

In this study, patients with Parkinson disease dementia (PDD), which is dementia that occurs in the context of well-established Parkinson disease, are not eligible. Therefore, the onset of dementia should not be greater than 1 year after onset of Parkinsonism. The investigator should determine the time of onset of Parkinsonian motor features based on clinical evaluation.

For assessment for cognitive function, the investigator should take into account scores of the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) used at screening.

In evaluation of the core clinical features, the investigator should take into account the scores in the Short Fluctuation Questionnaire (SFQ), Cognitive Fluctuation Inventory (CFI), Neuropsychiatric Inventory (NPI) and Unified Parkinson's Disease Rating Scale Part III: Motor Examination (UPDRS-III) for cognitive fluctuation, hallucinations and parkinsonian motor features respectively.

Indicative biomarkers include:

- Reduced dopamine transporter uptake in the basal ganglia on dopamine transporter (DAT) brain scan
- Abnormal (low uptake) in metaiodobenzylguanidine (MIBG) cardiac scan
- Polysomnography (PSG) confirmation of rapid eye movement (REM) sleep without atonia

When Parkinsonism is the only core feature of DLB in a patient with dementia, reduced DAT uptake warrants a probable DLB diagnosis provided that other disorders associated with cognitive impairment and reduced DAT uptake can be excluded.

Clinicians should carefully interpret MIBG results in the light of possible confounding causes, including ischemic heart disease, heart failure, diabetes mellitus, peripheral neuropathies, and medications that may cause reduced uptake including labetalol, reserpine, tricyclic antidepressants, and over-the-counter sympathomimetics.

Appendix 2 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 3 Examples of Adverse Events That May Signal Drug Abuse Potential

Examples of Adverse Events That May Signal Drug Abuse Potential

Categories			Examples[a]	
Euphoria-related terms	1	Euphoric mood	Euphoric mood	Feeling high
			Euphoria	Felt high
			Euphoric	High
			Exaggerated well-being	High feeling
			Excitement excessive	Laughter
	2	Elevated mood	Elevated mood	Elation
			Mood elevated	
	3	Feeling abnormal	Feeling abnormal	Funny episode
			Cotton wool in head	Fuzzy
			Feeling dazed	Fuzzy head
			Feeling floating	Muzzy head
			Feeling strange	Spaced out
			Feeling weightless	Unstable feeling
			Felt like a zombie	Weird feeling
			Floating feeling	Spacey
			Foggy feeling in head	
	4	Feeling drunk	Feeling drunk	Intoxicated
			Drunkenness feeling of	Stoned
			Drunk-like effect	Drugged
	5	Feeling of relaxation	Feeling of relaxation	Relaxed
			Feeling relaxed	Increased well-being
			Relaxation	Excessive happiness
	6	Dizziness	Dizziness	
	7	Thinking abnormal	Thinking abnormal	Thinking disturbance
			Abnormal thinking	Thought blocking

Examples of Adverse Events That May Signal Drug Abuse Potential

Categories			Examples[a]	
			Thinking irrational	Wandering thoughts
	8	**Hallucination**	Hallucination	Floating
			Illusions	Rush
			Flashbacks	Feeling addicted
	9	**Inappropriate affect**	Elation inappropriate	Inappropriate elation
			Exhilaration inappropriate	Inappropriate laughter
			Feeling happy inappropriately	Inappropriate mood elevation
			Inappropriate affect	
Terms indicative of impaired attention, cognition, and mood	10	**Somnolence**	Somnolence	
	11	**Mood disorders and disturbances**	Mental disturbance	Mood swings
			Depersonalisation	Emotional lability
			Psychomotor stimulation	Emotional disorder
			Mood disorders	Emotional distress
			Emotional and mood disturbances	Personality disorder
			Delirium	Impatience
			Delirious	Abnormal behavior
			Mood altered	Delusional disorder
			Mood alterations Mood instability	Irritability
Dissociative/psychotic terms	12	**Psychosis**	Psychosis	Psychotic episode or disorder
	13	**Aggression**	Aggression	
	14	**Confusion and disorientation**	Confusion and disorientation	
	15	**Dissociative State**	Dissociation	Detached
			Disconnected	Sensation of distance from one's environment
			Derealisation	Loss of a sense of personal identity

Examples of Adverse Events That May Signal Drug Abuse Potential

Categories			Examples[a]	
			Depersonalisation	
Related terms not captured elsewhere	**16**	**Drug tolerance**	Drug tolerance	
	17	**Habituation**	Habituation	
	18	**Substance related disorders**	Substance-related disorders	
Physical dependence or withdrawal[b]	**19**	**Drug withdrawal syndrome**	Drug withdrawal syndrome	Chills
			Headache	Decreased concentration
			Anxiety	Agitation
			Nausea	Irritability
			Vomiting	Sleep disturbances
			Tremor	Mood changes

a: Examples include terminology provided in the following guidance: U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry. Assessment of Abuse Potential of Drugs. January 2017. The same term may apply to more than 1 category. A more comprehensive list of terms is provided in the eCRF Completion Guidelines.

b: Only for events observed within the first 4 weeks of last dose of study drug.

Appendix 4 Cerebrospinal Fluid (CSF) Substudy (revised per Amendment 02)

This appendix describes the CSF substudy and consolidates the procedures for subjects who participate in the CSF substudy as already described in various sections of the main protocol.

Rationale

In the MAD Study 002, it was found that healthy subjects treated with E2027 at 50 mg QD for 6 weeks achieved CSF cGMP increase from baseline by ~220% and this was sustained from 2 weeks to 6 weeks. Internal data in Eisai suggested in subjects with DLB, there was ~17% reduction in CSF cGMP compared to healthy elderly subjects. Thus E2027 may increase neuronal cGMP in DLB subjects and improve cognition, but there may be differences in the PD response in DLB subjects compared to healthy subjects. Therefore this CSF substudy is undertaken to determine if E2027 achieves comparable CSF cGMP elevation as in healthy subjects, and will help to interpret any efficacy results on various cognitive or non-cognitive endpoints.

Exploratory Objectives

The CSF substudy aims to evaluate the effects of E2027 on CSF cGMP in subjects with DLB. The exploratory objectives are as described in Section 8.3:

- To explore the PK/PD relationship between the exposure of E2027 in CSF/plasma and its effects on CSF PD biomarker endpoints, including CSF cGMP, if data permit
- To explore the relationship between the E2027 PD effects (including CSF cGMP) with E2027 effects on various efficacy endpoints, if data permit

Eligibility Criteria

Inclusion Criteria:

- Subjects must meet all the inclusion criteria in Section 9.3.1.
- Provide separate informed consent for participation in the CSF substudy. If a subject lacks capacity to consent in the investigator's opinion, the subject's assent should be obtained, as required in accordance with local laws, regulations and customs, plus the written informed consent of a legal representative should be obtained (capacity to consent and definition of legal representative should be determined in accordance with applicable local laws and regulations).

Exclusion Criteria:

- All the exclusion criteria in Section 9.3.2 apply.
- Exclusion criterion 27 in Section 9.3.2 applies specifically to subjects participating in the CSF substudy, namely:

- A bleeding disorder that is not under adequate control (including a plate count <50,000, international normalized ratio [INR] >1.5 or partial thromboplastin time [PTT] > upper limit of normal [ULN]).
- Any contraindications to lumbar puncture (LP) (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, or obesity to the extent that it makes LP technically difficult).

Substudy Design

Participation in the CSF substudy is voluntary. Subjects who do not wish to participate in the CSF substudy may still participate in the main study without CSF collection. CSF will be collected by lumbar puncture (gravity drip method) during Screening and again during the Randomization Phase after 9 weeks of treatment on study drug.

Subjects who participate in the CSF substudy will undertake screening as described in Section 9.1.1. They will need to provide separate informed consent during screening before they can participate in the CSF substudy. Their informed consent for the CSF substudy should be provided at least 7 days before the Baseline Visit. After they have completed all screening assessments and are considered eligible for the study, they will have a blood test for clotting screen (PT, APTT, and INR) performed before the lumbar puncture (Table 6). If their clotting screen is satisfactory, then a baseline CSF sample will be collected at least 7 days before the Baseline Visit. If necessary, in these subjects the Screening Period may be extended by 1 week after discussion with the sponsor medical monitor.

Subjects in the CSF substudy then proceed to the Baseline Period (Section 9.1.2), followed by the Treatment Period (Section 9.1.3). After they have completed 9 weeks of treatment, they will have a 2nd CSF sample collected at Visit 7. The CSF samples will be collected in the morning at approximately the same time, either in the fasted state (preferred) or at least 2 hours after breakfast. The timing of the baseline CSF collection during screening needs to be scheduled carefully such that subsequent collection (at Visit 7) can be performed at a similar time of day (±2 hours) for each individual subject. Subjects will be encouraged to stay at the site after completion of LP for medical observation. If the LP and cognitive tests are performed on the same day, the LP must be performed after the cognitive tests are completed.

At Visit 7, a predose blood sample for PK will be taken first, followed by LP. Subjects will then be dosed with study drug and a PK sample will be collected at 1 – 4 hours postdose. If Visit 7 occurs after an ED Visit, blood PK samples and CSF will not be collected.

After completion of the Treatment Period, subjects will proceed to the Follow-Up Period (Section 9.1.4).

The study procedures for subjects who take part in the CSF substudy are already described in Table 6.

As data permit, CSF cGMP will be assayed to evaluate the PD effects of E2027 in these subjects with DLB. Other CSF PD biomarkers related to DLB or E2027 PD effects may also be assayed if appropriate. CSF E2027 concentrations will also be determined.

Prohibited and Restricted Concomitant Drugs

Prohibited or restricted concomitant drugs are described in Section 9.4.7.2. Specifically for subjects in the CSF substudy:

- Anticoagulants (eg, heparin, heparin derivatives, non-heparin derivatives, warfarin, dabigatran) and dual antiplatelet therapy (eg, aspirin and clopidogrel together) are prohibited from Screening Visit until after the 2nd CSF collection at 9 weeks postrandomization. These subjects who start anticoagulants or dual antiplatelet therapy at any time before CSF collection at 9 weeks postrandomization will not participate in the CSF substudy.

Risks of CSF Substudy

The local anesthetic may cause burning sensation, a local skin rash or irritation. The lumbar puncture may result in local pain / discomfort during the procedure.

The most common adverse effects from the lumbar puncture are headache and backache, caused by spinal fluid leaking from the puncture site. Approximately 10% of participants experience a headache and if a headache does occur, it usually improves while lying supine. The headache often resolves within 2 days, but in less than 5% of participants it can last longer. In subjects who have persistent, severe headache, injection of a blood patch may be required to stop the CSF leak.

Other possible known side effects of a lumbar puncture are listed below:

- Nausea
- Vomiting
- Dizziness
- Back pain or discomfort
- Infection
- Bleeding, bruising or leakage of spinal fluid from the puncture site
- Difficulty urinating
- Allergic reaction to local anesthetic
- Irritation to nerves with temporary numbness

Rare or very uncommon effects of lumbar puncture include low blood pressure, bleeding into the spinal canal, nerve damage or meningitis. These rare complications may be serious and could require hospitalization for urgent treatment, which may include antibiotics or surgery.

Statistical Analysis

Analysis of the primary efficacy endpoints, secondary efficacy endpoints, exploratory efficacy endpoints and safety endpoints in subjects in the CSF substudy will be conducted together with subjects who are not in the CSF substudy, as specified in Section 9.7.1.6 and Section 9.7.1.8.

As per Section 9.7.1.6.3, in subjects in the CSF substudy, if data permit, the relationship between E2027 PD effects on CSF cGMP (and other biomarkers) and various efficacy endpoints will be explored using correlation analysis and linear models will be fitted to further characterize the relationship between the changes in efficacy endpoints and the changes in E2027 PD variables as appropriate.

As per Section 9.7.1.7.2, data combining Phase 1 studies permitting, a population PK/PD approach will be used to characterize the relationship between plasma and/or CSF E2027 exposures and CSF PD biomarker levels. For this approach, data from this study will be pooled with relevant data from Phase 1 studies. The relationship between plasma and CSF E2027 exposure and the change from baseline of various efficacy endpoints will be explored graphically, as will the relationship between changes in CSF PD biomarkers and the change from baseline of various efficacy endpoints. Any emergent relationships will be explored through population PK/PD modeling.

The PK and PK/PD analyses will be detailed in a separate analysis plan and the results will be provided in a stand-alone report.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2027-G000-201
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Study To Evaluate the Efficacy, Safety and Tolerability of E2027 in Subjects With Dementia With Lewy Bodies
Investigational Product Name:	E2027
IND Number:	123614
EudraCT Number:	2017-003728-64

SIGNATURES

Authors:

PPD

PPD

Neurology Business Group
Eisai Ltd.

Date

PPD

PPD

Neurology Business Group
Eisai Inc.

Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2027-G000-201
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Study To Evaluate the Efficacy, Safety and Tolerability of E2027 in Subjects With Dementia With Lewy Bodies
Investigational Product Name:	E2027
IND Number:	123614
EudraCT Number:	2017-003728-64

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