Protocol I9X-MC-MTAE(e)

# Assessment of Safety, Tolerability, and Efficacy of LY3372689 in Early Symptomatic Alzheimer's Disease

NCT05063539

Approval Date: 22-Aug-2024

# Title Page



**Protocol Title:** Assessment of Safety, Tolerability, and Efficacy of LY3372689 in Early Symptomatic Alzheimer's Disease

**Protocol Number:** I9X-MC-MTAE

**Amendment Number:** e

**Compound:** LY3372689

**Study Phase:** 2

**Short Title:** Assessment of Safety, Tolerability, and Efficacy of LY3372689 in Early Symptomatic Alzheimer's Disease

**Sponsor Name:** Eli Lilly and Company

**Legal Registered Address:** Indianapolis, Indiana, USA 46285

**Regulatory Agency Identifier Numbers:**

IND: 141582

EudraCT: 2021-000170-29

EU CT number: 2024-512295-36-00

**Approval Date:** Protocol Amendment (e) Electronically Signed and Approved by Lilly on date provided below.

**Document ID:** VV-CLIN-007992

**Medical Monitor Name and Contact Information will be provided separately.**

# Protocol Amendment Summary of Changes Table

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Amendment d | 18-Apr-2024 |
| Amendment c | 22-Mar-2024 |
| Amendment b | 02-Sep-2021 |
| Amendment a | 09-Jun-2021 |
| Original Protocol | 06-Jan-2021 |

## Amendment [e]

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the safety or the rights of the study participants.

## Overall Rationale for the Amendment:

The main rationale for this amendment is the follow-up of safety findings and biomarker changes that emerged during the double-blind treatment period. The key changes include replacing the optional open-label extension (OLE) period with post-treatment safety follow-up period and removing the flortaucipir F18 PET imaging and MRI substudy.

Minor editorial and formatting changes are not included in this table.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis | • Deleted objective and endpoint of the OLE period<br>• Overall Design subsection: Deleted sentence regarding OLE consent and duration<br>• Intervention Groups and Duration subsection:<br>Revised study duration from "217" to "149" weeks<br>Deleted OLE period and safety follow-up (V802)<br>Added post-treatment safety follow-up period and corresponding duration | To align with the changes made to the study design (replacing the OLE period with post-treatment safety follow-up period) |
| 1.2. Schema | Deleted schema depicting OLE period and respective footnote | |
| 1.3.4. Study Period 4-Post-treatment Safety Follow-up Period | • Revised occurrence of OLE period to Post-treatment Safety Follow-up Period<br>• Deleted V31 through V802 (except V32) | |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | • Retained V32 as V803<br>• Revised ECG comments to read as: "single ECG with central reads"<br>• V802 (previously V30) changes: Added MRI imaging<br>• V803 (previously V31) changes: Added CDR, ADAS-Cog$_{13}$, ADCS-ADL, MMSE<br>• Laboratory Tests and Sample Collections row: Added comment for testosterone, LH, FSH and Inhibin B that it will be collected only in men<br>• Exploratory Biomarker Samples row: Added comments "Includes P-Tau"<br>• Deleted footnotes that are no longer applicable and re-arranged the sequence | |
| 3. Objectives and Endpoints | • Replaced the table for OLE period with objectives and endpoints for the post-treatment safety follow-up period | |
| 4.1. Overall Design | • Revised study duration from "217" to "149" weeks<br>• Deleted OLE period and safety follow-up (V802)<br>• Added post-treatment safety follow-up period and corresponding duration<br>• Deleted paragraph detailing specifics of the OLE period | |
| 4.1.5. Post-treatment Safety Follow-up Period | • Deleted paragraph on OLE period (V30-V37) and follow-up (V802)<br>• Added activities during the post-treatment safety follow-up period | |
| 4.2. Scientific Rationale for Study Design | Deleted paragraph on rationale for the OLE study design | |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.3. Justification for Dose | Deleted paragraph for the OLE dose selection | |
| 5.2. Exclusion Criteria | Deleted criterion 44, 45, and 46 | |
| 5.3. Post-Treatment Safety Follow-up Period (newly added section) | Added exclusion criterion 47 | |
| 6. Study Intervention | Deleted treatment regimen table for OLE period | |
| 6.3. Measures to Minimize Bias: Randomization and Blinding | • Deleted sentence "The extension phase of this study is open-label"<br>• Revised OLE period to Post-treatment Safety Follow-up Period in the last paragraph | |
| 6.5.1. Standard of Care for Alzheimer's Disease | Revised occurrence of OLE period to Post-treatment Safety Follow-up Period in the last paragraph and replaced the visits from "V30-V37" to "V802 and V803" | |
| 6.6. Dose Modification | Deleted last paragraph detailing dose modification during the OLE period | |
| 6.7. Intervention after the End of the Study | • Deleted statement that optional OLE will be offered to participants who complete the study through the double-blind study periods<br>• Added "study intervention will not be made available to participants after conclusion of the study" | |
| 9.4.1. General Considerations | • Revised occurrence of OLE period to Post-treatment Safety Follow-up Period<br>• Updated paragraph to capture the study will include 2 SAPs (previously several separate SAPs), and a supplemental SAP to detail additional exploratory analyses related to biomarkers | |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 10.10. Appendix 10: Flortaucipir F18 PET Imaging and MRI Substudy | Deleted substudy | |

**Table of Contents**

# 1. Protocol Summary

## 1.1. Synopsis

**Protocol Title:** Assessment of Safety, Tolerability, and Efficacy of LY3372689 in Early Symptomatic Alzheimer's Disease

**Short Title**: Assessment of Safety, Tolerability, and Efficacy of LY3372689 in Early Symptomatic Alzheimer's Disease

**Regulatory Agency Identifier Numbers:**

IND: 141582

EudraCT: 2021-000170-29

EU CT number: 2024-512295-36-00

**Rationale:**
LY3372689 is an orally available, potent inhibitor of O-linked N-acetyl glucosaminidase (OGA). This glycoside hydrolase is the enzyme that removes the single-sugar modification, O-linked β-N-acetyl glucosamine (O-GlcNAc), from intracellular proteins including the microtubule associated protein tau. This modification is regulated by the action of 2 enzymes, O-GlcNAc transferase (OGT) and OGA.

By inhibiting OGA, LY3372689 is hypothesized to delay the progression of tau aggregation-related diseases by slowing the accumulation of hyperphosphorylated, insoluble tau filaments within cells of the central nervous system (CNS), resulting in reduced propagation of tau pathology and preserved neuronal function.

**Objectives and Endpoints:**

| **Primary Objective** | **Endpoints[a]** |
|---|---|
| To assess the effect of LY3372689 vs. placebo on clinical progression in participants with early symptomatic AD with demonstrated presence of moderate[b] levels of tau pathology | iADRS change from baseline through end time point (76-124 weeks) |
| **Key Secondary Objective** | **Endpoints** |
| To assess the effect of LY3372689 vs. placebo on clinical progression in full study population (moderate + high[c] levels of tau pathology) with early symptomatic AD | iADRS change from baseline through end time point (76-124 weeks) |
| **Other Secondary Objectives** | **Endpoints** |
| To evaluate safety and tolerability of LY3372689 | Standard safety assessments<br>• Spontaneously reported AEs |

| | |
|---|---|
| | • Clinical laboratory tests<br>• Vital sign and body weight measurements<br>• 12-lead ECGs<br>• Physical and neurological examinations<br>• C-SSRS, and<br>• MRI (treatment-emergent radiological findings) |
| To assess the effect of LY3372689 vs. placebo on clinical progression in full study population and moderate tau sub population with early symptomatic AD | Change in cognition and function from baseline through end time point (76-124 weeks) as measured by:<br>• ADAS-Cog$_{13}$<br>• ADCS-iADL<br>• CDR-SB, and<br>• MMSE |
| To assess the effect of LY3372689 vs. placebo on brain region volumes | Change in volumetric MRI measures from baseline through end time point (76 - 124 weeks) |
| To assess the effect of LY3372689 vs. placebo on brain tau deposition | Change in brain tau deposition from baseline through end time point (76-100 weeks) as measured by flortaucipir F18 PET scan |
| To assess the PK of LY3372689 | Plasma concentrations of LY3372689 |

Abbreviations: ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living; AD = Alzheimer's Disease; AE = Adverse Event; CDR-SB = Clinical Dementia Rating Scale- Sum of Boxes; C-SSRS = Columbia Suicide-Severity Rating Scale; ECG = electrocardiograms; iADRS = integrated Alzheimer's Disease Rating Scale; MMSE = Mini Mental State Examination; MRI = Magnetic Resonance Imaging; PET = Positron emission tomography; PK = Pharmacokinetics.

[a] Based on common close design, participants final endpoint time will be between 76-124 weeks.

[b] Moderate tau pathology is defined as those who meet tau PET inclusion criteria for evidence of tau pathology consistent with Alzheimer's disease (Fleisher et al. 2020), but do not have widespread and high levels of cortical tau pathology.

[c] High levels of cortical tau pathology by flortaucipir F18 PET is defined by the top quartile of quantitative standardized uptake value ratios in a population of amyloid positive Alzheimer's participants and cognitively normal older controls (Pontecorvo et al. 2019).

**Overall Design:**

Study I9X-MC-MTAE (MTAE) is a multicenter, randomized, double-blind, placebo-controlled, Phase 2 study of LY3372689 in participants with early symptomatic Alzheimer's disease (AD). This study will utilize a 76-week common close design. Under the common close design, all enrolled participants will remain on double-blind randomized treatment and complete assessments until the last enrolled participant that has not discontinued from treatment has achieved 76 weeks of assigned treatment. The maximum duration of treatment is 124 weeks.

**Study Population:**

Eligible participants will have a gradual and progressive change in memory function with Mini Mental State Examination (MMSE) 22-30, Clinical Dementia Rating Scale (CDR) global score of 0.5 to 1.0, with a memory box score ≥0.5. Participants who meet plasma P-tau and flortaucipir F18 PET scan criteria will be eligible. Prior treatments with disease-modifying therapy or any commercially approved prescription medication for the treatment of AD, which meet study criteria are allowed. Participants who fail to complete the required psychometric tests, those with medical conditions, such as significant neurological disease affecting the CNS, cardiovascular, hepatic, renal, gastroenterological, respiratory, endocrinologic, neurologic, psychiatric, immunologic, hematologic disease, or cancer, may be excluded from participation in the study.

**Number of Participants:**

Approximately 110 participants will be randomly assigned per arm for a total of 330 randomized participants for study intervention.

**Intervention Groups and Duration:**

Participants who meet entry criteria will be randomized in a 1:1:1 (1 LY: 1 LY: 1 PBO) randomization to the following treatment groups:

- LY3372689: low dose daily
- LY3372689: high dose daily, and
- Placebo.

The maximum total duration of study participation for each participant, including screening and the post-treatment follow-up periods, is up to approximately 149 weeks:

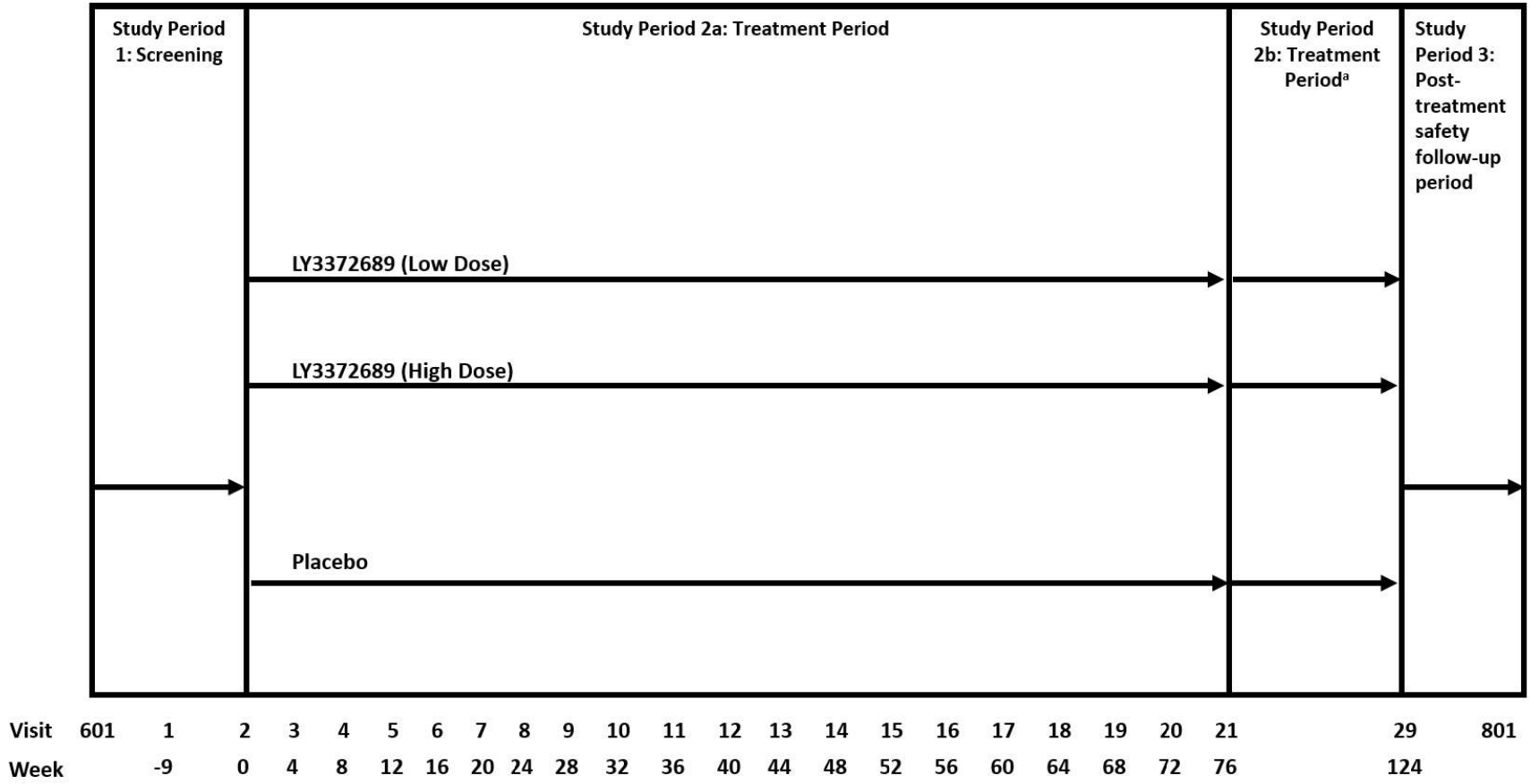
- Lead-In: complete any time prior to complete screening visit
- Complete Screening: -63 days to -1 day prior to randomization
- Double-Blind: 76 weeks or up to 124 weeks
- Safety Follow-up (V801): approximately 4 weeks after completion of double-blind study period 2b, and
- Post-treatment Safety Follow-up period: approximately 12 weeks and starts with Visit 802

**Ethical Considerations of Benefit/Risk:**

The available nonclinical and clinical data support the oral administration of LY3372689 to the intended study population according to the clinical investigation plan and also provide a sufficient margin of safety for the study design and doses. There are currently no disease-modifying anti-tau treatments for AD. The potential benefits of LY3372689 showing disease-modifying properties in participants with AD are considered to outweigh the potential risks.

**Data Monitoring Committee: Yes**

## 1.2. Schema




[a] Study I9X-MC-MTAE (MTAE) has a common close design in which all enrolled participants continue to study Period 2b until the last enrolled participant that has not discontinued from treatment reaches 76 weeks of treatment. The maximum study treatment period length will be 124 weeks.

## 1.3. Schedule of Activities (SoA)

### 1.3.1. Study Period 1-Screening

| Study Period 1- Screening[a] | | | |
|---|---|---|---|
| | **LEAD-IN SCREENING** | **COMPLETE SCREENING** | **Comments** |
| **Visit No.:** | 601 | 1 | |
| **Days Relative to Randomization** | Can be done any time prior to V1 | -63 to -1 (≤63 before V2) | |
| **Tolerance Interval for Visit (Days)** | Can be done any time | ≤63 before V2 | |
| **Entry and Administrative** | | | |
| Abbreviated or full informed consent (participant and study partner) | X | | The abbreviated informed consent grants consent only for procedures and assessments marked under V601.<br>Study partner(s) is(are) not required to complete the abbreviated informed consent form. |
| Full informed consent (participant and study partner) | | X | Do not collect if full informed consent was collected at V601. |
| Inclusion and exclusion criteria, review, and confirm | | X | Confirm that the participant has met all V1 eligibility criteria before proceeding to V2 procedures. |
| Demographics | X | X | Do not collect demographics at V1 if collected at V601. |
| Preexisting conditions and medical history, including relevant surgical history | | X | |
| Prespecified medical history (indication and history of interest) | | X | |
| Substance use (alcohol, caffeine, and tobacco use) | | X | |
| Concomitant medications | | X | |
| AEs | | X | |

| Study Period 1- Screening[a] | | | |
|---|---|---|---|
| | **LEAD-IN SCREENING** | **COMPLETE SCREENING** | **Comments** |
| **Visit No.:** | 601 | 1 | |
| **Days Relative to Randomization** | Can be done any time prior to V1 | -63 to -1 (≤63 before V2) | |
| **Tolerance Interval for Visit (Days)** | Can be done any time | ≤63 before V2 | |
| **Physical Evaluation** | | | |
| Height | | X | |
| Weight | | X | |
| Vital signs | | X | BP, pulse, and temperature (after 5 min in sitting position). |
| Physical examination | | X | |
| 12-lead ECG (central) | | X | Triplicate ECG |
| **PET Scans and MRI** | | | |
| Flortaucipir F18 PET scan[b,c,d] | | X | A historical flortaucipir F18 PET scan may be submitted to be considered for eligibility if performed within 6 months of randomization. The acceptance of a historical scan is at the discretion of the sponsor. |
| MRI[b,d] | | X | |
| **Clinician-Administered Assessments (Electronic)[e]** | | | |
| CDR | | X | The CDR must always be administered to the study partner first and then to the participant. |
| MMSE | X | X | Do not perform MMSE at V1 if collected at V601, unless >3 months since V601. |
| **Laboratory Tests and Sample Collections** | | | |
| Hematology | | X | |
| Clinical chemistry | | X | |
| Hepatitis B virus (HBV) Screening tests | | X | Perform at screening in participants with a past history (suspected or confirmed) of Hepatitis B. |
| Hepatitis C virus (HCV) Screening tests | | X | Perform at screening in participants with a past history (suspected or confirmed) of Hepatitis C (resolved >6 months prior to enrollment). |

| Study Period 1- Screening[a] | | | |
|---|---|---|---|
| | **LEAD-IN SCREENING** | **COMPLETE SCREENING** | **Comments** |
| **Visit No.:** | 601 | 1 | |
| **Days Relative to Randomization** | Can be done any time prior to V1 | -63 to -1 (≤63 before V2) | |
| **Tolerance Interval for Visit (Days)** | Can be done any time | ≤63 before V2 | |
| Plasma P-tau[d] | X | X | Do not collect plasma P-tau at V1 if collected at V601. Historical evidence of AD pathology may be accepted for eligibility at the discretion of the sponsor. A plasma sample should be collected for all participants, regardless of whether or not the site is approved to use P-tau testing as part of eligibility determination. |
| **Stored Samples** | | | |
| Genetics sample | | X | Collect unless not allowed or unfeasible due to local regulations. |
| Exploratory biomarker samples | X | X | Collect unless not allowed or unfeasible due to local regulations. Do not collect exploratory biomarker samples at V1 if collected at V601. |

Abbreviations: AD = Alzheimer's Disease; AE = adverse event; BP = blood pressure; CDR = Clinical Dementia Rating Scale; C-SSRS = Columbia Suicide Severity Rating Scale; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; PET = positron emission tomography; V = Visit.

[a] Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance.

[b] The participant should meet all other eligibility criteria before the screening flortaucipir F18 PET scan and MRI.

[c] If results are received after the 63-day screening period, the participant remains eligible contingent on meeting the other eligibility criteria. May require review and/or retest of screening safety labs if >63 days between V1 and V2.

[d] If plasma P-tau testing is not available to the site for eligibility determination at the time of screening, the sample should still be collected and submitted. In such cases, the participant may proceed to screening flortaucipir F18 PET scan and MRI if all other screening requirements are met, with no requirement to document plasma P-tau eligibility results. Sites will be notified if this situation applies. This will not be considered a protocol deviation.

[e] Administer prior to medical procedures that could be stressful to the participant (blood draws, etc.). These tests include the audio voice recording of the rater's questions and the participant and study partner responses to assessment questions.

### 1.3.2. Study Period 2a-Treatment Period

| | Study Period 2a - Treatment period [a] | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit No.:** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **ET (Period 2a)** | **Comments** |
| **Weeks Relative to Randomization** | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 76 | | |
| **Remote Visit Option** | | | | | | | | | | | | X | | | | X | | | X | | | Remote home visits are an option to on-site visit. |
| **Televisits** | | | | | | | | | | | X | | X | | X | | | X | | | | Visits are to be performed by phone. |
| **Tolerance interval for visit (Days)** | 0 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | | |
| Randomization | X | | | | | | | | | | | | | | | | | | | | | |
| Inclusion and exclusion criteria | X | | | | | | | | | | | | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| AEs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| **Physical Evaluation** | | | | | | | | | | | | | | | | | | | | | | |
| Weight | X | | | X | | | X | | | X | | | | X | | | X | | | X | X | |
| Vital signs | X | X | X | X | X | X | X | X | X | X | | X | | X | | X | X | | X | X | X | BP, pulse, and temperature (after 5 min in sitting position). In addition, orthostatic BP and pulse will be measured at V2, V5, V8, V11, V15, V18, V21, ET, and unscheduled visits. |
| Physical/neuro examination | X | X | | X | | | X | | | X | | | | X | | | X | | | X | X | |

| | Study Period 2a - Treatment period [a] | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit No.:** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **ET (Period 2a)** | **Comments** |
| **Weeks Relative to Randomization** | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 76 | | |
| **Remote Visit Option** | | | | | | | | | | | | X | | | | X | | | X | | | Remote home visits are an option to on-site visit. |
| **Televisits** | | | | | | | | | | | X | | X | | X | | | X | | | | Visits are to be performed by phone. |
| **Tolerance interval for visit (Days)** | 0 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | | |
| Symptom-directed physical examination | | | X | | X | X | | X | X | | | X | | | | X | | | X | | | |
| 12-lead ECG (central) | X | X | X | X | X | X | X | | | X | | | | X | | | X | | | X | X | Single ECG |
| **PET Scans and MRI** | | | | | | | | | | | | | | | | | | | | | | |
| Flortaucipir F18 PET scan | | | | | | | | | | | | | | | | | | | | X | X [b] | No more than one PET scan should be obtained in Period 2a. |
| MRI | | | | | | | | | | | | | | X | | | | | | X | X [c] | MRI not performed if <24 weeks since last MRI. |
| **Clinician-Administered Assessments (Electronic) [d]** | | | | | | | | | | | | | | | | | | | | | | |
| ADAS-$Cog_{13}$ | X | | | X | | | X | | | X | | | | X | | | X | | | X | X [e] | |
| ADCS-ADL | X | | | X | | | X | | | X | | | | X | | | X | | | X | X [e] | |
| CDR | | | | X | | | X | | | X | | | | X | | | X | | | X | X [e] | The CDR must always be administered to the study partner first and then to the participant. |
| MMSE | X [f] | | | X | | | X | | | X | | | | X | | | X | | | X | X [e] | |

| | Study Period 2a - Treatment period [a] | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit No.:** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **ET (Period 2a)** | **Comments** |
| **Weeks Relative to Randomization** | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 76 | | |
| **Remote Visit Option** | | | | | | | | | | | | X | | | | X | | | X | | | Remote home visits are an option to on-site visit. |
| **Televisits** | | | | | | | | | | | X | | X | | X | | | X | | | | Visits are to be performed by phone. |
| **Tolerance interval for visit (Days)** | 0 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | | |
| DSST | X | X | X | X | X | X | X | | | X | | | | X | | | X | | | X | X[e] | |
| Digital clock | X | X | X | X | X | X | X | | | X | | | | X | | | X | | | X | X[e] | |
| **Clinician-Administered Assessments (Paper)** | | | | | | | | | | | | | | | | | | | | | | |
| C-SSRS baseline | X | | | | | | | | | | | | | | | | | | | | | |
| C-SSRS since last visit | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| **Laboratory Tests and Sample Collections[g]** | | | | | | | | | | | | | | | | | | | | | | |
| Hematology | X | X | X | X | | | X | | | X | | | | X | | | X | | | X | X | |
| Clinical chemistry | X | X | X | X | | | X | | | X | | | | X | | | X | | | X | X | |
| Urinalysis | X | | | | | | X | | | | | | | X | | | | | | X | X | |
| Estrogen [h] | X | | | X | | | X | | | | | | | | | | | | | | X[i] | |
| Testosterone[h] | X | | | X | | | X | | | | | | | | | | | | | X | X[i] | |
| LH[h] | X | | | X | | | X | | | | | | | | | | | | | X | X[i] | |
| FSH[h] | X | | | X | | | X | | | | | | | | | | | | | X | X[i] | |
| Inhibin B[h] | X | | | X | | | X | | | | | | | | | | | | | X | X[i] | |
| ApoE[j] | X | | | | | | | | | | | | | | | | | | | | | |
| PK sample | X[k] | X[l] | X | | | | X | | | X | | | | X | | | X | | | | X[m] | |

| | Study Period 2a - Treatment period [a] | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit No.:** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **ET (Period 2a)** | **Comments** |
| **Weeks Relative to Randomization** | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 76 | | |
| **Remote Visit Option** | | | | | | | | | | | | X | | | | X | | | X | | | Remote home visits are an option to on-site visit. |
| **Televisits** | | | | | | | | | | | X | | X | | X | | | X | | | | Visits are to be performed by phone. |
| **Tolerance interval for visit (Days)** | 0 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | | |
| **Exploratory Endpoint and Stored Samples** | | | | | | | | | | | | | | | | | | | | | | |
| Exploratory biomarker samples [j] | X | | | X | | | X | | | X | | | | X | | | X | | | X | X | |
| **Randomization and Dosing** | | | | | | | | | | | | | | | | | | | | | | |
| Contact IWRS | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Dispense study drug | X | X | X | X | X | X | X | X | X | X | | X | | X | | X | X | | X | X[n] | | Drug to be dispensed at prior in-person visit for televisits |
| Administer study drug at site | X[o] | X | | | | | | | | | | | | | | | | | | | | |
| Participant returns study drug | | X | X | X | X | X | X | X | X | X | | X | | X | | X | X | | X | X | X | |
| Assess study drug compliance | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |

Abbreviations: ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living; AE = Adverse Event; ApoE = Apolipoprotein E; BP = blood pressure; ECG = electrocardiogram; CDR = Clinical Dementia Rating Scale; C-SSRS = Columbia Suicide Severity Rating Scale; DSST = Digit Symbol Substitution Test; ET = Early Termination; FSH = Follicle Stimulating Hormone; IP = Investigational Product; IWRS = interactive web-response system; LH = Luteinizing Hormone; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetics; V = Visit

[a] Procedures for some visits may take more than 1 day. For early terminations that occur before the last visit in treatment period, see the activities listed for ET in this table.

[b] ET PET scan if on study drug for at least 12 weeks. Participants who discontinue treatment but remain in the study off IP should receive imaging as scheduled and should not receive an ET PET scan unless the ET visit coincides with Week 76.

[c] ET MRI scan is only performed if it is at least 24 weeks since last MRI assessment.

[d] Administer the ADAS-Cog13, ADCS-ADL, CDR, MMSE, DSST, and Digital Clock prior to medical procedures that could be stressful to the participant (blood draws, etc.). These tests include the audio voice recording of the rater's questions and the participant and study partner responses to assessment questions.

[e] For participants who permanently discontinued from IP but remain in the study, cognitive assessments should be performed only if they coincide with a protocol-defined study window where cognitive testing would have otherwise occurred during Period 2a as defined by the SoA.
For participants who permanently discontinue from IP and the study, cognitive assessments should be performed only if >10 weeks since the last cognitive assessments.

[f] MMSE not to be performed at V2 if done at V1 or within 3 months of V601.

[g] Unscheduled lab tests may be performed at the discretion of the investigator. Collect labs prior to administration of IP, unless otherwise noted. Record the date and times of sample collection on the Lab Requisition Form.

[h] Hormone panel to be collected in the morning. From Weeks 76 through 124 and V801, hormone panel would be collected only in men.

[i] Collect if ET coincides with a protocol-defined study window where hormone panel collection would have otherwise occurred.

[j] Collect unless not allowed or unfeasible due to local regulations.

[k] At V2, take PK sample within 0.5-4 h after drug administration.

[l] At V3, take the first PK sample prior to receiving drug at site, and second PK sample after receiving drug at site but prior to participant leaving the site.

[m] Collect a PK sample at ET only if participant is discontinued due to an AE. At ET, the PK sample should be taken following clinician-administered assessments.

[n] Dispensed at V21 if participant is continuing on to Period 2b.

[o] All V2 baseline clinical assessments and testing should be performed prior to study drug administration at site.

### 1.3.3. Study Period 2b-Treatment Period

| | Study Period 2b - Common Close (or Treatment Beyond Week 76) [a] | | | | | | | | | Study Period 3-Post-treatment safety follow-up period | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit No.:** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **ET (Period 2b) [b]** | V801 4 weeks±10 days after participant's last Study Period 2 visit | **Comments** |
| Weeks relative to Randomization | 82 | 88 | 94 | 100 | 106 | 112 | 118 | 124 | | | |
| Televisit | X | | X | | X | | X | | | | Visits to be performed by phone. |
| Tolerance interval for visit (days) | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | |
| AEs | X | X | X | X | X | X | X | X | X | X | |
| **Physical Evaluation** | | | | | | | | | | | |
| Weight | | X | | X | | X | | X | X | X | |
| Vital signs | | X | | X | | X | | X | X | X | BP, pulse, and temperature (after 5 min in sitting position). In addition, orthostatic BP and pulse will be measured at V23, V25, V27, V29, and ET. |
| Physical/neuro examination | | X | | X | | X | | X | X | X | |
| 12-lead ECG (central) | | X | | X | | X | | X | X | X | Single ECG. |
| **PET Scans and MRI** | | | | | | | | | | | |
| Flortaucipir F18 PET scan | | | | X | | | | | X[c] | | No more than one PET scan should be obtained in Period 2b. |
| MRI | | | | X | | | | X | X[d] | | MRI not performed if <24 weeks since last MRI assessment. |
| **Clinician-Administered Assessments (Electronic) [e]** | | | | | | | | | | | |
| ADAS-Cog$_{13}$ | | X | | X | | X | | X | X[f] | | |
| ADCS-ADL | | X | | X | | X | | X | X[f] | | |

| | Study Period 2b - Common Close (or Treatment Beyond Week 76) [a] | | | | | | | | | Study Period 3-Post-treatment safety follow-up period | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit No.:** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **ET (Period 2b)** [b] | V801 4 weeks±10 days after participant's last Study Period 2 visit | **Comments** |
| Weeks relative to Randomization | 82 | 88 | 94 | 100 | 106 | 112 | 118 | 124 | | | |
| Televisit | X | | X | | X | | X | | | | Visits to be performed by phone. |
| Tolerance interval for visit (days) | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | | | |
| CDR | | X | | X | | X | | X | X[f] | | The CDR must always be administered to the study partner first and then to the participant. |
| MMSE | | X | | X | | X | | X | X[f] | | |
| DSST | | X | | X | | X | | X | X[f] | | |
| Digital Clock | | X | | X | | X | | X | X[f] | | |
| **Clinician-Administered Assessments (Paper)** | | | | | | | | | | | |
| C-SSRS Since Last Visit | X | X | X | X | X | X | X | X | X | X | |
| **Laboratory Tests and Sample Collections**[g] | | | | | | | | | | | |
| Hematology | | X | | X | | X | | X | X | X | |
| Clinical chemistry | | X | | X | | X | | X | X | X | |
| Urinalysis | | | | | | | | | X | X | |
| PK sample | | | | | | | | | X[h] | | |
| Testosterone[i] | | X | | X | | X | | X | X | X | Collected only in men |
| LH[i] | | X | | X | | X | | X | X | X | |
| FSH[i] | | X | | X | | X | | X | X | X | |
| Inhibin B[i] | | X | | X | | X | | X | X | X | |
| **Exploratory Endpoint and Stored Samples** | | | | | | | | | | | |
| Exploratory Biomarker Samples[j] | | X | | X | | X | | X | X | | |

| | Study Period 2b - Common Close (or Treatment Beyond Week 76) [a] | | | | | | | | | Study Period 3-Post-treatment safety follow-up period | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit No.:** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **ET (Period 2b) [b]** | V801 4 weeks±10 days after participant's last Study Period 2 visit | **Comments** |
| Weeks relative to Randomization | 82 | 88 | 94 | 100 | 106 | 112 | 118 | 124 | | | |
| Televisit | X | | X | | X | | X | | | | Visits to be performed by phone. |
| Tolerance interval for visit (days) | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | | | |
| **Randomization and Dosing** | | | | | | | | | | | |
| Contact IWRS | X | X | X | X | X | X | X | X | X | X | |
| Dispense study drug | | X | | X | | X | | | | | Drug to be dispensed at prior in-person visit for televisits |
| Participant returns study drug | | X | | X | | X | | X | X | | |
| Assess study drug compliance | X | X | X | X | X | X | X | X | X | | |

Abbreviations: ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living; AE = Adverse Event; BP = blood pressure; CDR = Clinical Dementia Rating Scale; C-SSRS = Columbia Suicide Severity Rating Scale; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; ET = Early Termination; IP = Investigational Product; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetics; V = Visit.

[a] All participants are to complete Period 2a and continue to period 2b/3 unless otherwise notified by sponsor. Procedures for some visits may take more than 1 day. For early terminations that occur before the last visit in treatment period, see the activities listed for ET in this table.

[b] For participants in Period 2b at the time of the common close (that is, when the last participant completes 76 weeks of treatment), the ET visit activities are to be conducted as the next and final Period 2b visit, the End-of-Study ET Visit.

[c] ET PET scan only to be performed if ET occurs at Week 100 ± 7 days and Visit 25 PET scan did not occur.

[d] ET MRI scan is only performed if it is at least 24 weeks since last MRI assessment.

[e] Administer the ADAS-Cog$_{13}$, ADCS-ADL, CDR, MMSE, DSST, and Digital Clock prior to medical procedures that could be stressful to the participant (blood draws, etc.). These tests include the audio voice recording of the rater's questions and the participant and study partner responses to assessment questions.

[f] For participants who permanently discontinue from IP but remain in the study, cognitive assessments should be performed only if they coincide with a protocol-defined study window where cognitive testing would have otherwise occurred during Period 2b as defined by the SoA.
For participants who permanently discontinue from IP and the study, cognitive assessments should be performed only if >10 weeks since the last cognitive assessments.
When the last enrolled participant that does not discontinue reaches week 76, all remaining participants will be in Period 2b and should complete an end-of-study ET visit at that time. At this visit, cognitive assessments should be performed only if they coincide with a protocol-defined study window where cognitive testing would have otherwise occurred as defined by the SoA or if it has been >10 weeks since the last assessment.

[g] Unscheduled lab tests may be performed at the discretion of the investigator. Collect labs prior to administration of IP, unless otherwise noted. Record the date and times of sample collection on the Lab Requisition Form.

[h] Collect a PK sample at ET only if participant discontinues treatment due to an AE. At ET, the PK sample should be taken following clinician-administered assessments.

[i] Hormone panel to be collected in the morning. From Weeks 76 through 124 and V801, hormone panel would be collected only in men.

[j] Collect unless not allowed or unfeasible due to local regulations.

### 1.3.4. Study Period 4-Post-treatment Safety Follow-up Period

**Note:** All randomly assigned participants are eligible for participation.

| **Visit No.:** | **802** | **803** | **Comments** |
|---|---|---|---|
| Weeks | 0 | 12 | |
| Tolerance interval for visit (days) | ±7 | ±7 | |
| Informed consent (participant and study partner) | X | | Reconsent must be completed prior to initiating Visit 802 procedures. |
| Concomitant medications | X | X | |
| AEs | X | X | |
| **Physical Evaluation** | | | |
| Weight | X | X | |
| Vital signs | X | X | |
| Physical/neuro examination | X | | |
| Symptom-directed physical examination | | X | |
| 12-lead ECG (central) | X | X | Single ECG with central reads. |
| **Imaging** | | | |
| MRI | X | | |
| **Clinician-Administered Assessments (Electronic)[a]** | | | |
| CDR | X | X | The CDR must always be administered to the study partner first and then to the participant. |
| ADAS-Cog$_{13}$ | X | X | |
| ADCS-ADL | X | X | |
| MMSE | X | X | |
| **Clinician-Administered Assessments (Paper)** | | | |
| C-SSRS Since Last Visit | X | X | |
| **Laboratory Tests and Sample Collections[b]** | | | |
| Hematology | X | X | |
| Clinical chemistry | X | X | |
| Testosterone[c] | X | X | Collected only in men. |
| LH[c] | X | X | |
| FSH[c] | X | X | |
| Inhibin B[c] | X | X | |

| Visit No.: | 802 | 803 | Comments |
|---|---|---|---|
| Weeks | 0 | 12 | |
| Tolerance interval for visit (days) | ±7 | ±7 | |
| **Exploratory Endpoint and Stored Samples** | | | |
| Exploratory Biomarker Samples[d] | X | X | Includes P-Tau. |

Abbreviations: ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living; AE = adverse event; CDR = Clinical Dementia Rating Scale; ECG = electrocardiogram; ET = early termination; C-SSRS = Columbia Suicide Severity Rating Scale; ET = Early Termination; FSH = follicle stimulating hormone; IWRS = interactive web-response system; LH = luteinizing hormone; MMSE = mini mental state examination; OLE = open-label extension; PK = pharmacokinetics; V = Visit.

[a] Administer the ADAS-Cog13, ADCS-ADL, CDR, and MMSE prior to medical procedures that could be stressful to the participant (for example, blood draws). These tests include the audio voice recording of the rater's questions and the participant and study partner responses to assessment questions.

[b] Unscheduled laboratory tests may be performed at the discretion of the investigator. Collect labs prior to administration of IP, unless otherwise noted. Record the date and times of sample collection on the Lab Requisition Form.

[c] Hormone panel to be collected in the morning.

[d] Collect unless not allowed or unfeasible due to local regulations.

# 2. Introduction

## 2.1. Study Rationale

AD is an age-related neurodegenerative disorder characterized by a progressive decline in cognitive function and ability to perform activities of daily living that ultimately leads to death due to complications of the disease. Pathologic hallmarks of AD identified at autopsy include the presence of neuritic amyloid-β plaques, tau neurofibrillary tangles (Hyman et al. 2012), and neuronal loss, particularly pronounced in brain regions important for cognition, such as the hippocampus and temporal cortex (Selkoe 1991). Extent and pattern of tau pathology closely tracks with cognitive symptoms in AD (Brier et al. 2016; Pontecorvo et al. 2019). The current Study MTAE aims to demonstrate that LY3372689 slows cognitive and functional decline, and to assess safety of chronic administration, in early symptomatic AD participants demonstrating evidence of tauopathy. For the purposes of this study, early symptomatic AD is defined as those with mild cognitive impairment due to AD or mild Alzheimer's dementia, consistent with stages 2 through 4 of the FDA draft guidance entitled "*Early Alzheimer's Disease: Developing Drugs for Treatment. Guidance for Industry*" (February 2018; https://www.fda.gov/media/110903/download) and the *NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease* (Jack et al. 2018).

## 2.2. Background

OGA is a glycoside hydrolase enzyme that removes the single-sugar modification O-GlcNAc from intracellular proteins, such as microtubule-associated protein tau. OGA inhibitors increase tau O-GlcNAc levels by blocking the removal of this single-sugar from unbound tau protein. This inhibition has been shown to reduce the accumulation of hyperphosphorylated, insoluble tau, including neurofibrillary tangles, in animal models of tauopathy (Yuzwa et al. 2014; Graham et al. 2014; Hastings et al. 2017).

LY3372689 is an orally available, potent inhibitor of OGA and is hypothesized to delay the progression of tau-related diseases by slowing the accumulation of hyperphosphorylated, insoluble tau filaments within cells of the CNS, resulting in reduced propagation of tau pathology and preserved neuronal function. Reduction of tau propagation is hypothesized to slow clinical progression of people diagnosed with early symptomatic AD.

### 2.2.1. Nonclinical Studies

Nonclinical studies demonstrate that LY3372689 engages the OGA enzyme target in vivo, inhibits OGA enzyme activity, and increases the levels of protein O-GlcNAc and tau O-GlcNAc levels in the brain of mice and rats after single and multiple doses. Treatment with another proprietary aminothiazole compound reduced pathologic tau in the forebrain of the P301S tau transgenic mouse model following chronic (3 months) dosing.

In vitro metabolism studies suggest that CCI [redacted]. Solubility and permeability data for LY3372689 are consistent with Biopharmaceutics Classification System Class 1-like compounds.

The toxicity of LY3372689 has been characterized in GLP nonclinical safety studies in Sprague-Dawley rats and beagle dogs, including 9-month (dogs), 6-month (rats), 28-day, and 2-day repeat-dose general toxicology studies, as well as genetic toxicology and safety pharmacology studies. The 9-month and 6-month repeat-dose toxicity studies included 13-week reversibility periods. The 28-day repeat-dose toxicity studies included an 8-week reversibility period in dogs and a 13-week reversibility period in rats. The 2-day repeat-dose toxicity studies included a 14-day reversibility period in both species. Developmental and reproductive toxicology (DART) studies were performed in rats and rabbits.


### 2.2.2. Clinical Studies

Overall LY3372689 has been evaluated in 4 Phase 1 studies. These studies included healthy participants from Studies MTAA, MTAB, MTAC, and MTAD. LY3372689 was administered as a single dose in Studies MTAA and MTAB and as repeat doses for 14 days in Studies MTAC and MTAD. The safety data indicate that LY3372689 was well tolerated. To date, 71 healthy participants received at least 1 dose of LY3372689. In these 4 studies, no deaths or SAEs were reported. One discontinuation due to an AE was reported, influenza type A in Study MTAC, and was not considered related to the study drug by the investigator.

The SAD Study MTAA was a Phase 1, placebo-controlled, randomized study in 23 healthy male and female participants (15 males, 8 females; aged 22 to 63 years). Participants received LY3372689 (0.15 to 16 mg) and placebo in a crossover manner, over 3 study periods. Safety and PK data were collected for 7 days in each period. LY3372689 exposure based on AUC0-∞ and

$C_{max}$ increased in a generally dose-proportional manner from 0.6 to 16 mg. Safety data indicated that LY3372689 was well tolerated when administered as a single dose up to 16 mg.

Study MTAB was a single-dose PET study utilizing [18F]LY3316612 PET tracer to assess enzyme occupancy (EO), and to establish the relationship between plasma LY3372689 concentration and EO, after single oral doses of LY3372689. Sixteen healthy males were dosed 0.25, 1, or 5 mg across 4 cohorts, with 4 participants within each cohort. The EO was assessed at 2 and 24 h post-dose at all doses, as well as 30 h and 54 h post-dose at 1 mg only. In general, a dose- and concentration-dependent change in EO was observed. At 1 and 5 mg, near maximum EO (97% to 98%) was observed at 2 h post-dose. The EO at 5 mg declined slightly from 98% at 2 h to 93% at 24 h post-dose. At 1 mg, the EO declined from 97% at 2 h, to 81% at 24 h, to 30% at 54 h post-dose. The EO at 0.25 mg was 26% at 2 h and 46% at 24 h. The PK profile of LY3372689 in this study was similar to what was observed in the prior single-dose SAD Study. Safety data indicated that LY3372689 was well tolerated up to 5 mg.

Study MTAC was a Multiple Ascending Dose (MAD), placebo-controlled, randomized study in women of non-childbearing potential, vasectomized males, and 7 Japanese participants as a subgroup. LY3372689 was administered at doses of 1, 3, and 7 mg given QD for 14 days. Following repeat dosing, there was a small degree of accumulation of LY3372689 with a relative accumulation of 1.06-1.34 across the dose range. The impact of food was also tested which showed no effect on the extent of exposure but a 43% decrease in $C_{max}$ with a delay in $t_{max}$ by 5 h, compared to the fasted state. In terms of safety, there was no dose dependency in incidence or severity for treatment-emergent AEs. There were no clinically significant changes in ECGs, including no evidence of QTc, nor PR interval prolongation. There were also no clinically significant changes in vital signs, neurological examinations, or safety laboratory tests, including male hormones.

Study MTAD was an open-label, nonrandomized, multiple-dose PET study, utilizing [18F]LY3316612 to assess OGA brain EO resulting from oral doses of LY3372689 administered QD for 14 days in a single cohort of 4 healthy participants. PET scans were conducted approximately 24 h after the first administration (on Day 1) and last administration (on Day 14) of 1 mg LY3372689 given QD for 14 days. Initial results show no change in enzyme occupancy from Day 1 to Day 15 of the study. These data provide confidence that brain OGA EO can be sustained with multiple dosing. Overall, no dose-dependent relationship in incidence or severity of treatment-related AEs was observed, and blood markers of inflammation or muscle injury were within normal limits. There were no clinically significant changes in vital signs, ECGs, neurological examinations, or safety laboratories, including male hormone panel and creatinine kinase.

## 2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3372689 may be found in the IB.

**Potential Risks of Clinical Significance**

CCI


**Mitigation Strategy**


**Summary/Rationale for Risk**

In summary, the available nonclinical and clinical safety data support administration of LY3372689 in the intended study population. The noted risk mitigation strategy allows for careful monitoring for potential AEs.

### 2.3.1. Benefit Assessment

There is a large unmet medical need for disease-modifying treatments for AD. Animal models suggest that OGA inhibition will reduce progression or spread of the aggregated forms of tau. In addition to the assessment of safety and tolerability of LY3372689, this study will also assess whether inhibition of OGA and potential reduction in aggregated tau can slow the progression of the disease as assessed by clinical measures and biomarkers of disease pathology and neurodegeneration relative to placebo treatment.

### 2.3.2. Overall Benefit/Risk Conclusion

In conclusion, the available nonclinical and clinical data support the oral administration of LY3372689 to the intended study population according to the clinical investigation plan and also provide a sufficient margin of safety for the study design and doses. There are currently no disease-modifying anti-tau treatments for AD. The potential benefits of LY3372689 showing disease-modifying properties in participants with AD are considered to outweigh the potential risks.

# 3. Objectives and Endpoints

| **Primary Objective** | **Endpoints[a]** |
|---|---|
| To assess the effect of LY3372689 vs. placebo on clinical progression in participants with early symptomatic AD with demonstrated presence of moderate[b] levels of tau pathology | iADRS change from baseline through end time point (76-124 weeks) |
| **Key Secondary Objective** | **Endpoints** |
| To assess the effect of LY3372689 vs. placebo on clinical progression in full study population (moderate + high[c] levels of tau pathology) with early symptomatic AD | iADRS change from baseline through end time point (76-124 weeks) |
| **Other Secondary Objectives** | **Endpoints** |
| To evaluate safety and tolerability of LY3372689 | Standard safety assessments<br>• Spontaneously reported AEs<br>• Clinical laboratory tests<br>• Vital sign and body weight measurements<br>• 12-lead ECGs<br>• Physical and neurological examinations<br>• C-SSRS, and<br>• MRI (treatment-emergent radiological findings) |
| To assess the effect of LY3372689 vs. placebo on clinical progression in full study population and moderate tau sub population with early symptomatic AD | Change in cognition and function from baseline through end time point (76-124 weeks) as measured by:<br>• ADAS-$Cog_{13}$<br>• ADCS-iADL<br>• CDR-SB, and<br>• MMSE |
| To assess the effect of LY3372689 vs. placebo on brain region volumes | Change in volumetric MRI measures from baseline through end time point (76 - 124 weeks) |
| To assess the effect of LY3372689 vs. placebo on brain tau deposition | Change in brain tau deposition from baseline through end time point (76-100 weeks) as measured by flortaucipir F18 PET scan |
| To assess the PK of LY3372689 | Plasma concentrations of LY3372689 |

| **Exploratory Objectives** | **Endpoints** |
|---|---|
| To assess the effect of LY3372689 vs placebo on blood-based biomarkers | Change from baseline through end time point (76-124 weeks) on blood-based biomarkers of AD pathology and neurodegeneration |
| To assess the effect of LY3372689 vs placebo on additional assessments of cognition | Change from baseline through end time point (76-124 weeks) as measured by:<br>• Digital Clock Drawing Test, and<br>• DSST |
| To explore the relationship between tau burden and clinical outcomes | Tau burden<br>• Blood-based biomarkers, and<br>• Flortaucipir F18 PET<br>Clinical outcomes<br>• ADAS-$Cog_{13}$<br>• ADCS-iADL<br>• CDR-SB<br>• iADRS, and<br>• MMSE |
| To explore the relationship between blood-based biomarkers and imaging | Blood-based biomarkers of AD pathology and neurodegeneration<br>Imaging<br>• Flortaucipir F18 PET, and<br>• MRI |
| To assess the efficacy of LY3372689 to prolong time to clinical progression | CDR global score |

Abbreviations: ADAS-$Cog_{13}$ = Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living; AD = Alzheimer's Disease; AE = Adverse Event; CDR-SB = Clinical Dementia Rating Scale-Sum of Boxes; C-SSRS = Columbia Suicide-Severity Rating Scale; ECG = electrocardiograms; iADRS = integrated Alzheimer's Disease Rating Scale; MMSE = Mini Mental State Examination; MRI = Magnetic Resonance Imaging; PET = Positron emission tomography; PK = Pharmacokinetics.

[a] Based on common close design, participants final endpoint time will be between 76-124 weeks.

[b] Moderate tau pathology is defined as those who meet tau PET inclusion criteria for evidence of tau pathology consistent with Alzheimer's disease (Fleisher et al. 2020), but do not have widespread and high levels of cortical tau pathology.

[c] High levels of cortical tau pathology by flortaucipir F18 PET is defined by the top quartile of quantitative standardized uptake value ratios in a population of amyloid positive Alzheimer's participants and cognitively normal older controls (Pontecorvo et al. 2019).

**Post-Treatment Safety Follow-up Period**

| Objectives | Endpoints |
|---|---|
| To assess clinical effects after previous treatment with LY3372689 on clinical progression in participants with early symptomatic AD who participated in the double-blind treatment periods | Change in cognitive and functional assessments:<br>• iADRS<br>• ADAS-Cog13<br>• ADCS-iADL<br>• CDR-SB, and<br>• MMSE |
| To assess safety effects after previous treatment with LY3372689 | Standard safety assessments<br>• spontaneously reported AEs<br>• MRI (treatment-emergent radiological findings)<br>• clinical laboratory tests<br>• vital sign and body weight measurements<br>• 12-lead ECGs<br>• physical and neurological examinations, and<br>• C-SSRS |
| To assess effect after previous treatment with LY3372689 on brain region volumes | Volumetric MRI measures |
| To assess effect after previous treatment with LY3372689 on blood-based biomarkers | Change from baseline through end time point on blood-based biomarkers of AD pathology and neurodegeneration |

Abbreviations: ADAS-$Cog_{13}$ = Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS- iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living; AD = Alzheimer's disease; AE = adverse event; CDR-SB = Clinical Dementia Rating Scale-Sum of Boxes; C-SSRS = Columbia Suicide-Severity Rating Scale; ECG = electrocardiogram; iADRS = integrated Alzheimer's Disease Rating Scale; MMSE = mini mental state examination; MRI = Magnetic Resonance Imaging.

# 4. Study Design

## 4.1. Overall Design

Study MTAE is a multicenter, randomized, double-blind, placebo-controlled, Phase 2 study of LY3372689 in participants with early symptomatic AD. Participants who meet entry criteria will be randomized in a 1:1:1 (1 LY: 1 LY: 1 PBO) randomization of the following treatment groups:

- LY3372689: low dose once daily
- LY3372689: high dose once daily, and
- Placebo.

The maximum total duration of study participation for each participant, including screening and the post-treatment follow-up periods, is up to approximately 149 weeks:

- Lead-In: complete any time prior to complete screening visit
- Complete Screening: -63 days to -1 day prior to randomization
- Double-Blind: 76 weeks or up to 124 weeks
- Safety Follow-up (V801): approximately 4 weeks after completion of double-blind study period 2b, and
- Post-treatment Safety Follow-up Period: approximately 12 weeks and starts with Visit 802

This study will utilize a 76-week common close design. Under the common close design, all enrolled participants will remain on double-blind randomized treatment and complete assessments until the last enrolled participant that has not discontinued from treatment has achieved 76 weeks of assigned treatment. The maximum duration of treatment is 124 weeks.

### 4.1.1. Lead-In and Screening Period (V601 and V1)

At or before Visit 1, the study will be explained to the participant (and his or her legal representative, if applicable) and study partner. Informed consent must be obtained before any study procedures are conducted. The lead-in period (V601) is optional and may occur any time prior to Visit 1.

The screening period spans the time between Visit 1 to Visit 2.

For those who participate in V601, a preliminary screening informed consent or full study consent will be obtained to conduct lead-in screening to collect demographics data, administer the MMSE, and collect a blood sample for plasma phosphorylated tau (P-tau). The P-tau assay is an investigational device. Participants who do not meet the MMSE screening criteria are not to have any other screening procedures performed. For rescreening instructions, see Section 5.5. Participants who meet both MMSE and plasma P-tau screening criteria (where available) or have other evidence of AD pathology (approved by sponsor) may proceed to the remaining V1 screening procedures once they have given signed or dated informed consent for the full study. Plasma P-tau testing may not be available at all locations for screening purposes. At these sites, a P-tau blood sample should still be collected and submitted. In such cases, only MMSE criteria must be met to proceed to V1.

For V1, once the full informed consent is signed, 63 days are allowed for completion of the remaining Visit 1 screening assessments and procedures, as described in the SoA (Section 1.3). For those who do not complete V601 prior to signing full study consent and proceed directly to V1, MMSE and CDR screening criteria will need to be met before proceeding to have blood samples collected for plasma P-tau, other lab testing, and performing other cognitive assessments. The MRI and flortaucipir F18 PET scans are to be performed only after the participant meets all other eligibility criteria in the complete screening visit (V1). For sites at which P-tau testing will not be available as a screening procedure, it will not be a protocol deviation to continue with flortaucipir F18 PET scanning without meeting the P-tau screening criterion. In such cases, P-tau results will not be required for randomization and enrollment if all other screening criteria are met. Although imaging may be the last screening procedures of the study, it is expected that the centrally read results will be available within the timeframe of 63 days. However, it will not be a protocol deviation, should imaging screening results not be available until after 63 days. Participants whose screening imaging results are not available until after 63 days will remain eligible within Visit 1 until these results become available.

Visit 1 is not considered complete until all required screening procedures have been completed, results have been reviewed by the investigator or qualified designee, and the investigator or qualified designee has confirmed that the participant is eligible to be randomized. Only then can the participant proceed to Visit 2.

### 4.1.2. Double-Blind Period 2a (V2-21)

The treatment period 2a is a double-blind treatment phase beginning at Visit 2 (randomization). At Visit 2, appointments should be made for all remaining visits and should be scheduled as close as possible to the target date, relative to Visit 2. Participants who meet entry criteria and proceed to Visit 2 will be enrolled and randomized to receive up to 124 weeks of treatment with LY3372689 low dose, LY3372689 high dose, or placebo. During this double-blind period, participants will take study drug tablets once daily as dispensed. Assessments and procedures will be performed as indicated in the SoA (Section 1.3). Procedures for some visits may take more than 1 day.

All participants that continue assessments in the study will have a minimum of 76 weeks of study assessments. All participants except the last enrolled participant that has not discontinued from the study will continue to Study Period 2b. The last enrolled participant that has not discontinued from the study will have their last visit with final assessments occurring at week 76 (V21). Sites will be notified if a participant at their site is to have their study completion visit at week 76, otherwise all participants should continue to study Period 2b (V22-29).

### 4.1.3. Double-Blind Period 2b (V22-29)

All participants other than the last enrolled participant, who has a study completion visit at V21, will continue with assessments and procedures as indicated in the SoA for Study Period 2b. The final visit for participants in Study Period 2b will occur when the last enrolled participant that has not discontinued from the study completes their V21 study completion visit. At that time, all participants in study Period 2b will undergo a study completion visit (end-of-study ET visit) at their next scheduled visit (following the instructions for the Period 2b ET visit) as described in the SoA and Manual of Operations. Study sponsor will notify sites when the last enrolled

participant achieves study completion V21, to enable scheduling of end of study ET visits for Period 2b. End-of-study ET visits will follow assessments as indicated by the ET visit in Period 2b (see SoA; Section 1.3).

#### 4.1.4. Follow-up (V801)

Participants are to return to the site for safety follow-up visit (Visit 801) 4 weeks ±10 days after the last double-blind treatment visit has occurred. Assessments are to be performed as indicated in the SoA (Section 1.3).

#### 4.1.5. Post-Treatment Safety Follow-up Period (V802 and V803)

Participants will be offered the opportunity to participate in the post-treatment safety follow-up period. Participants are to return to the site for post-treatment safety follow-up visit which lasts for approximately 12 weeks and starts at Visit 802. Assessments are to be performed as indicated in the SoA (Section 1.3.4).

### 4.2. Scientific Rationale for Study Design

Study MTAE is a multicenter, randomized, double-blind, placebo-controlled study of LY3372689 in participants with early symptomatic AD, MMSE 22-30, CDR-global score of 0.5-1.0, with cerebral tau burden that is elevated, as measured by flortaucipir F18. For the purposes of this study, early symptomatic AD is defined as those with mild cognitive impairment due to AD or mild Alzheimer's dementia, consistent with Stages 2 through 4 of the FDA draft guidance entitled "*Early Alzheimer's Disease: Developing Drugs for Treatment. Guidance for Industry*" (February 2018; https://www.fda.gov/media/110903/download) and the *NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease*. (Jack et al. 2018).

Study MTAE includes a placebo treatment arm and allows all participants to continue their AD standard-of-care concomitant medications. The use of a placebo comparator in Study MTAE is needed to determine the efficacy and safety of LY3372689 therapy. Inclusion of a placebo treatment arm is acceptable in Study MTAE because there are no available disease-modifying anti-tau treatments for AD; this approach is in agreement with the use of placebo described in the Declaration of Helsinki (WMA 2013).

The study includes a screening visit, which can last up to 63 days from the time of signing the full ICF, at which participants are required to have plasma tau (where available) and flortaucipir F18 PET imaging results consistent with the presence of elevated tau pathology in order to be randomized to the double-blind period. A common close study design is used to maximize efficiency by increasing overall duration of treatment in the study population without increasing the overall length of the study. This is intended to result in increased likelihood of detecting LY3372689 effects on study endpoints while minimizing overall study length and number of enrolled participants.

See Section 8.1 for descriptions of outcome measures. In addition to clinical outcomes, imaging biomarkers will also be measured to assess the direct effect of LY3372689 on brain atrophy and aggregated tau neurofibrillary tangle accumulation over time, which are a known hallmark pathologies of AD, and hypothesized to contribute to the cognitive and functional decline in people with AD. Tau pathology is theorized to be a mediator for clinical decline and therefore it

is hypothesized that the reduction of tau aggregation and further propagation may slow clinical decline.

## 4.3. Justification for Dose

Doses of 0.75 mg QD (low dose) and 3 mg QD (high dose) are being administered to assess a comparison of efficacy and safety compared to placebo in this study. The dose justification for the study rests on characteristics of the nonclinical safety and pharmacology profile, and pharmacokinetic (PK), pharmacodynamic (PD), and safety findings in healthy human volunteers. Specifically, OGA EO was assessed in the brain of healthy participants using a novel PET radiotracer [$^{18}$F] LSN3316612 after single oral doses of LY3372689 ranging from 0.25 to 0.5 mg, and after once daily dosing of 1 mg for 14 days. There was a dose- and concentration-dependent change in OGA brain EO, which was maintained with multiple dosing up to 14 days. Based on PK/PD modeling, a dose of 0.75 mg is predicted to achieve at trough a median EO of 84% with a 62% probability of achieving 80%, and 3 mg is predicted to achieve at trough a median EO of 95% with a 98% probability of achieving 80% EO. To note, brain EO of 80% was shown in preclinical animal models to reduce tau pathology and used as a benchmark to optimize doses for this clinical trial in AD participants.

Overall, doses of 0.75 and 3 mg once daily were selected because both doses are predicted to achieve at trough an EO of >80%. The lower dose has the potential for improved safety profile relative to a higher dose based on nonclinical toxicology findings (Section 2.2.1), with the higher dose of 3 mg providing near maximum EO to fully interrogate the OGA inhibition mechanism of action and test the OGA hypothesis. Furthermore, 3 mg in this study is less than the top dose of [redacted] mg in the single ascending dose study and [redacted] mg in the MAD study studies (Section 2.2.2), which in both studies did not demonstrate any dose-limiting AEs.

If during study conduct the external DMC recommends dose reduction at the study arm level, the high-dose arm could be reduced to 1.5 mg (Section 6.6).

## 4.4. End of Study Definition

A participant is considered to have completed the study if he or she has completed all required phases of the study including the last visit or the last scheduled procedure shown in the SoA.

# 5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Early symptomatic AD participants, as defined in the inclusion criteria (Section 5.1), will be enrolled into Study MTAE. The inclusion criteria ensure that participants meet clinical criteria for having an AD clinical syndrome and have biomarker evidence consistent with the presence of AD pathology (Jack et al. 2018). With the use of tau PET imaging, with or without plasma P-Tau levels, as part of the eligibility criteria, enrolled participants will be highly likely to meet pathological criteria for AD, including the presence of both key pathologies, brain amyloid plaque and aggregated tau neurofibrillary tangles. (Fleisher et al. 2020; Palmqvist et al. 2020). This study population is hypothesized to represent those that will most benefit from the mechanism of action of LY3372689, which is believed to reduce further accumulation of pathological tau but not remove existing tau; further, a population at the earlier stages of tau pathology may benefit the most from LY3372689 treatment. It is also necessary to enroll a population that is likely to demonstrate clinical decline in the timeframe of Study MTAE. Elevated levels of tau pathology have been associated with increased risk for clinical progression (Pontecorvo et al. 2019). Therefore, the inclusion criteria for Study MTAE are selected to identify a study population with known tau pathology targeted by LY3372689, at levels consistent with risk of short-term clinical progression.

## 5.1. Inclusion Criteria

**Participant Characteristics**

[1] Men or women (not of childbearing potential), 60 to 85 years of age.

a. Female participants are considered women not of childbearing potential if
   - they have a congenital anomaly, such as Mullerian agenesis, or
   - they are infertile due to surgical sterilization (e.g., hysterectomy, or at least 6 weeks post-surgical bilateral oophorectomy or tubal ligation), or
   - they are post-menopausal.

b. The post-menopausal state is defined as
   i. a woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or
   ii. a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[2] Gradual and progressive change in memory function reported by the participant or informant for ≥6 months.

[3] MMSE 22-30 (inclusive).

[4] CDR global score of 0.5 to 1.0 (inclusive), with a memory box score ≥0.5.

[5] Meet plasma P-tau criteria (where available for screening purposes). The acceptance of a historical evidence of positive AD pathology in the place of plasma P-tau is at the discretion of the sponsor.

[6] Meet flortaucipir F18 PET scan criteria. A historical flortaucipir F18 PET scan may be submitted to be considered for eligibility if performed within 6 months of randomization. The acceptance of a historical scan is at the discretion of the sponsor.

[7] Have a study partner who will provide written informed consent to participate, is in frequent contact with the participant (defined as at least 10 h per week), and will accompany the participant to study visits or be available by telephone at designated times.
A second study partner may serve as backup. The study partner(s) is(are) required to accompany the participant for signing consent. One study partner is requested to be present on all days the C-SSRS is administered and must be present on all days the cognitive and functional scales are administered. If a participant has a second study partner, it is preferred that 1 study partner be primarily responsible for the CDR and the ADCS-ADL assessments. Visits not requiring CDR must have a study partner available by telephone if not accompanying participant at a visit for the following assessments:

- AEs and concomitant medications, and
- relevant portions of the C-SSRS

If a study partner must withdraw from study participation, a replacement may be allowed at the investigator's discretion. The replacement will need to sign a separate informed consent on the first visit that he or she accompanies the participant.

[8] Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

[9] Males who agree to use effective methods of contraception may participate in this trial.

Contraception

a. Male participants

(i). should refrain from sperm donation for the duration of the study and until 92 days following the last dose of study drug.

(ii). regardless of their fertility status, with nonpregnant female partners of childbearing potential, must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms with spermicide during intercourse for the duration of the study and for 92 days after study drug dosing.

(iii). who are in exclusively same sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

[10] If taking a commercially approved prescription medication for the treatment of AD, have received treatment with a stable dose for at least 1 month before screening (V1). If approved prescription medication for AD is a disease-modifying therapy (e.g., anti-amyloid or anti-tau), then have received treatment with a stable dose for at least 3 months prior to V2. If a participant has recently stopped an approved AD medication, he or she must have discontinued treatment at least 2 months or >5 half-lives (whichever is longer) of the medication before randomization.

[11] Changes in concomitant medications that could potentially affect cognition and their dosing should be stable for at least 1 month before screening, and between screening and randomization (does not apply to medications discontinued due to exclusions or with limited duration of use, such as antibiotics).

**Informed Consent**

[12] Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

## 5.2. Exclusion Criteria

[13] Lack, in the investigator's opinion, of adequate premorbid literacy, adequate vision, or adequate hearing to complete the required psychometric tests.

[14] Significant neurological disease affecting the CNS, other than AD, that may affect cognition or ability to complete the study, including but not limited to, other dementias, serious infection of the brain, Parkinson's disease, multiple concussions, or epilepsy or recurrent seizures (except febrile childhood seizures).

[15] Current serious or unstable illnesses including cardiovascular, hepatic, renal, gastroenterological, respiratory, endocrinologic (including unstable diabetes), neurologic (other than AD), psychiatric, immunologic, or hematologic disease and other conditions that, in the investigator's opinion, could interfere with the analyses in this study; or has a life expectancy of <24 months.

[16] History of cancer within the last 5 years, with the exception of nonmetastatic basal and/or squamous cell carcinoma of the skin, in situ cervical cancer, nonprogressive prostate cancer, or other cancers with low risk of recurrence or spread.

[17] Participants with any current primary psychiatric diagnosis other than AD if, in the judgment of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessment, or affect the participant's ability to complete the study. Participants with a history of schizophrenia or other chronic psychosis are excluded.

[18] Are clinically judged by the investigator to be at serious risk for suicide as assessed by medical history, or examination.

[19] History of alcohol or drug abuse disorder (except tobacco use disorder) within 2 years before the screening visit.

[20] Known positive serologic findings for human immunodeficiency virus antibodies. Local laws and regulations may apply to whether testing is required.

[21] Participants with a past history (suspected or confirmed) of Hepatitis B should have HBsAg testing at screening and are excluded if HBsAg is positive.

[22] Participants with a past history (suspected or confirmed) of Hepatitis C (resolved >6 months prior to enrollment) should have HCV RNA PCR testing at screening and are excluded if the HCV RNA PCR test is positive.

[23] History of clinically significant multiple or severe drug allergies, significant atopy, or severe posttreatment hypersensitivity reactions (including but not limited to erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, and/or exfoliative dermatitis).

**Imaging, Vital Signs, Electrocardiograms, Laboratory Tests, and Physical Examination**

[24] Have any clinically important abnormality at screening, as determined by the investigator, in physical or neurological examination, vital signs, ECG, or clinical laboratory test results that could be detrimental to the participant, could compromise the study, or show evidence of other etiologies for dementia.

[25] Screening MRI that shows evidence of significant abnormality that would suggest another potential etiology for progressive dementia or a clinically significant finding that may impact the participant's ability to safely participate in the study.

[26] Have any contraindications for MRI, including claustrophobia or the presence of contraindicated metal (ferromagnetic) implants/cardiac pacemaker.

[27] Sensitivity to flortaucipir F18.

[28] Contraindication to PET and present or planned exposure to ionizing radiation that, in combination with the planned administration of study PET ligands, would result in a cumulative exposure that exceeds local recommended exposure limits.

[29] Cardiovascular screening ECG criteria

- heart rate less than 45 beats/min
- Mobitz type 2 second-degree or third-degree AV block (uncorrected by cardiac pacemaker), and
- ECG with QTc >450 msec in males and >470 msec in females.

[30] Calculated creatinine clearance <30 mL/min (Cockcroft–Gault formula; Cockcroft and Gault 1976) at screening.

[31] ALT ≥2x the ULN of the performing laboratory, AST ≥2x ULN, TBL ≥2x ULN, or ALP ≥2x ULN at screening.

NOTE: Participants with TBL ≥2x ULN are not excluded if they meet all of the following criteria for Gilbert syndrome:

a. bilirubin is predominantly indirect (unconjugated) at screening (direct bilirubin within normal limits).

b. absence of liver disease.

c. ALT, AST, and ALP ≤1x ULN at screening.

d. hemoglobin is not significantly decreased at screening.

**Prior/Concomitant Therapy** (Refer to Manual of Operations for complete lists)

[32] Have known allergies to LY3372689, related compounds, or any components of the formulation; or history of significant atopy.

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**Prior/Concurrent Clinical Trial Experience**

[35] Are currently enrolled in any other interventional clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[36] Have participated within the last 30 days in a clinical trial involving an investigational product. If the previous investigational product is scientifically or medically incompatible with this study (such as an anti-tau or anti-amyloid therapy) and has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed prior to screening. Participation in observational studies may be permitted upon review of the observational study protocol and approval by the sponsor.

**Other Exclusions**

[37] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[38] Are Lilly employees or are employees of TPOs involved in the study who require exclusion of their employees, or have study partners who are Lilly employees or are employees of TPOs involved in a study that requires exclusion of their employees.

[44] Criterion deleted.

[45] Criterion deleted.

[46] Criterion deleted.

## 5.3. Post-Treatment Safety Follow-up Period

**Exclusion criteria**

[47] Are currently enrolled in any other interventional clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

## 5.4. Lifestyle Considerations

Participants should refrain from donating blood or blood products from the time of their screening visit until 7 days following the last dose of IP.

Participants should avoid excessive use of alcohol from the screening visit until the study ends. Excessive alcohol consumption is defined for men as consuming an average of more than 3 drinks per day, or more than 21 drinks per week. For women, excessive use of alcohol is defined as consuming an average of more than 2 drinks per day, or more than 14 drinks per week.

## 5.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

If the screen failure is due to a CDR global score <0.5, or due to non-eligible plasma P-tau or flortaucipir F18 PET scan, then 1 rescreen will be allowed after 24 weeks.

Other reasons for screen failure will require sponsor approval for rescreen.

# 6. Study Intervention

Study intervention is defined as any medicinal product(s) or medical device(s) intended to be administered to or used by a study participant according to the study protocol.

## 6.1. Study Intervention(s) Administered

**Treatment Regimens, Double-Blind Treatment Period**

| LY3372689 Dose (mg) | Regimen |
|---|---|
| 0.75 | LY3372689: 0.75 mg dose once daily for up to 124 weeks (minimum of 76 weeks) (Visit 2 [Week 0]–Visit 29 [Week 124]). |
| 3.0[a] | LY3372689: 3.0 mg dose once daily for up to 124 weeks (minimum of 76 weeks) (Visit 2 [Week 0]–Visit 29 [Week 124]). |
| Placebo | Placebo dose once daily for up to 124 weeks (minimum of 76 weeks) (Visit 2 [Week 0]–Visit 29 [Week 124]). |

[a] Dose may be reduced from 3 to 1.5 mg if deemed necessary. Refer to Section 6.6.

Investigational products used in this study are:

- LY3372689, and
- Placebo.

Investigational products are administered orally once daily in the morning at approximately the same time each day. LY3372689 may be taken with or without food. All LY3372689 strengths and placebo will be identical tablets.

This study will utilize a 76-week common close design. Under the common close design, all enrolled participants will remain on double-blind randomized treatment and complete assessments until the last enrolled participant that has not discontinued from treatment has achieved 76 weeks of assigned treatment. The maximum duration of treatment is 124 weeks.

The table below lists the study interventions used in this clinical study.

| **Intervention Name** | LY3372689 | Placebo | Flortaucipir F18 |
|---|---|---|---|
| **Authorized as defined by EU Clinical Trial Regulation** | Not authorized | Not authorized | Not authorized |

**Packaging and Labeling**

Study intervention will be supplied by the sponsor or designee in accordance with current Good Manufacturing Practice. Clinical trial materials will be labeled according to the country's regulatory requirements. All IPs will be stored, inventoried, reconciled, and destroyed according to applicable regulations. Clinical trial materials are manufactured in accordance with current Good Manufacturing Practices.

## 6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.
2. Only participants enrolled in the study may receive IP, and only authorized site staff or designee may supply or administer IP. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff or designee.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for IP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused IP are provided by the sponsor.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

This is a double-blind study (study periods 2a and 2b), with design to maintain blinding to treatment. To preserve the blinding of the study, a minimal number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

For between-group comparability, participant randomization will be stratified by the investigative site, tau burden (moderate versus high) as defined by flortaucipir PET, and by prior or current use of any approved disease-modifying therapy for AD. Enrollment of high tau burden participants will be capitated at a predetermined proportion of the total enrolled population. Hence, study eligibility based on flortaucipir PET scan results may change as the study progresses. Assignment to treatment groups will be determined using an interactive web response system (IWRS). The IWRS will be programmed using the dynamic allocation (minimization) method of Pocock and Simon (1975), to balance the treatment arms using three factors: investigative site, tau burden, and prior or current use of any approved disease-modifying therapy for AD. This is to achieve balanced participant assignment between treatment arms as much as possible within each stratum and at the study level. Randomization into 1 stratum may be discontinued at the discretion of the sponsor.

Blinded site personnel will dispense study intervention and confirm that they have located the correct packages by entering a confirmation number found on the label into the IWRS.

The independent external DMC is unblinded to randomization.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a Lilly-designated Medical Monitor for the participant to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, Lilly must be notified immediately. If the

investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Participants who meet all criteria for enrollment will be assigned a study (participant) number at Visit 601 or Visit 1 and randomized to double-blind treatment at Visit 2. Participants will be randomized to LY3372689 low dose, LY3372689 high dose, or Placebo in a 1:1:1 ratio.

Participants will remain blinded to the original treatment arms while participating in the post-treatment safety follow-up period.

## 6.4. Study Intervention Compliance

Participant compliance with study medication will be assessed at each visit by direct questioning and/or counting returned tablets. The participant should be instructed to retain all empty drug packages after using up the medication in the package and to bring the empty packages and any unused medication to the clinic at each visit so that the clinic staff can record the amount of medication used since the last visit.

Compliance for the double-blind study periods will be assessed at telephone visits via questioning of the participant and/or study partner.

The administration of all study medication should be recorded in the appropriate sections of the eCRF.

Participants who consume 80-100% of the prescribed daily dose during this study will be considered compliant. A participant will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more or less than the prescribed amount of medication. Participants regarded as non-compliant may be discontinued at the investigator's discretion, in consultation with the Lilly-designated Medical Monitor.

## 6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the CRF, along with any changes to dose.

The Lilly-designated Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants and their study partners will be instructed to consult the investigator or other appropriate study personnel at the site before initiation of any new medications or supplements and before changing dose of any current concomitant medications or supplements.

Use of benzodiazepines for treatment on an as-needed basis for insomnia or daily dosing as anxiolytics is permitted. Use of sedatives or hypnotics should be avoided for 8 h before administration of the cognitive and functional tests unless they are given chronically.

The following are prohibited concomitant medications during the study (refer to Manual of Operations for complete lists):

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- Use of any investigational drug or device not specified in this study unless approved by the Lilly-designated medical monitor (topical may be permitted)
- Use of any drug of abuse, including but not limited to illicit amphetamine, cocaine, illicit opiates, propoxyphene, methadone, methaqualone, phencyclidine, and illicit barbiturate.
- Use of cannabis in a pattern of abuse.

### 6.5.1. Standard of Care for Alzheimer's Disease

To ensure standard of care for AD, use of approved prescription treatments for AD is permitted (but not a requirement) in this study. The section below provides additional guidance on managing concomitant medication use.

**Double-Blind Period (Period 2a and 2b)**

Use of approved or standard-of-care treatments for AD is permitted (but not a requirement) during the study, provided that the dose has been unchanged for 1 month before Visit 1. If approved prescription AD medication is a disease-modifying therapy (e.g., anti-amyloid or anti-tau), then dose must be stable for at least 3 months prior to V2. Doses of these medications should remain constant when possible, throughout the double-blind period (Visit 2 to 29). Any initiation or changes to standard-of-care medications should be done in consultation with the sponsor prior to implementing to determine if the participant would be allowed to continue in the study.

Nonmedication treatments for AD such as behavioral management are permitted but are subject to the same restrictions as medication treatment taken for AD.

**Post-treatment Safety Follow-up Period (V802 and V803)**

Use of approved or standard-of-care treatments including both symptomatic and disease-modifying therapies are permitted during the post-treatment safety follow-up period. Any changes to concomitant medication should be documented. Any concomitant medication used should be approved and used per the direction of the prescribing information.

## 6.6. Dose Modification

Dose modification of IP will be permitted for notable treatment-emergent AEs and AEs of special interest as determined by the study sponsor medical team, or as determined by the unblinded external DMC recommendations. Sponsor, site staff, and study participant will remain blinded to treatment assignments in all cases. A one-time dose reduction can be applied in a blinded fashion after sponsor safety review and/or an external DMC review (blinded or unblinded) on a case-by-case basis. Individual case dose reductions will result in individual participant reductions from 3.0 to 1.5 mg, or 0.75 mg to placebo, depending on the blinded treatment arm assignment of the participant. No change will be made for participants assigned to the placebo arm. If safety concerns remain for individual participants after dose reduction, a permanent discontinuation of study drug may be necessary. Based on a scheduled or ad-hoc safety review, the external DMC may also opt to trigger a dose reduction for the entire high-dose arm from 3.0 mg to a pre-established reduction dose of 1.5 mg for those participants assigned to the high-dose arm. There are no pre-established dose reductions for the low-dose arm. Study

team, participants, and blinded site staff will remain blinded to study dose and treatment arm in the event of dose reductions. In addition, treatment can be temporarily discontinued as an alternative to a dose reduction (see Section 7.1.1).

## 6.7. Intervention after the End of the Study

Study intervention will not be made available to participants after conclusion of the study.

# 7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

## 7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue IP. If IP is permanently discontinued, the participant may remain in the study (following the SoA, except as noted below) to be evaluated for safety and efficacy.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation for ET procedures and follow-up and for any further evaluations that need to be completed.

Participants who permanently discontinued from IP but remain in the study should complete ET procedures (as indicated in the SoA), then continue to participate in subsequent scheduled visits and assessments, as appropriate. After ET visit, PK assessments should not be collected in participants that have permanently discontinued from IP.

Investigational product may be discontinued for a participant for the following reasons (details given below):

- clinical judgment
- AEs
- by request of the participant or participant's designee (e.g., legal guardian)
- severe noncompliance
- the participant requires an excluded therapeutic agent and temporary discontinuation criteria cannot be met, and
- pacemaker that is not MRI-compatible.

Clinical Judgment

AE or clinically significant laboratory value, ECG result, physical examination finding, MRI finding (such as symptomatic ischemic stroke), C-SSRS result, or vital sign measurement of such severity that, in the opinion of the investigator or Lilly-designated Medical Monitor, continued treatment is not in the best interest of the participant.

Hepatic Event or Liver Test Abnormality

Participants who are discontinued from IP due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via the CRF.

Discontinuation of the IP for abnormal liver tests should be considered by the investigator when a participant meets 1 of the following conditions after consultation with the Lilly-designated Medical Monitor:

- ALT or AST >8x ULN
- ALT or AST >5x ULN for more than 2 weeks
- ALT or AST >3x ULN and TBL >2x ULN or INR >1.5
- ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3x ULN
- ALP >2.5x ULN and TBL >2x ULN

- ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

C-SSRS

In addition, IP may be discontinued if participants:

- Answer "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, or
- Answer "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.

ECG

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using QTcF, PR interval or new onset AV block) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Severe Noncompliance

Severe noncompliance to the study protocol, that results in a safety concern, in the judgment of the investigator, may be reason for discontinuing IP.

Excluded Therapeutic Agent

The participant, for any reason, requires a treatment with an excluded therapeutic agent (Section 6.5) and temporary discontinuation criteria cannot be met (see Section 7.1.1).

Pacemaker that is not MRI-compatible

Participants who require a ferromagnetic implant or insertion of a cardiac pacemaker that is not MRI-compatible will be discontinued from IP and may remain in the study off IP with no further MRIs.

### 7.1.1. Temporary Discontinuation

Treatment can be temporarily discontinued (examples include short-term treatment using a prohibited drug, uncertain AE, hospitalization). Re-starting investigational product is based on Sponsor and the Principal Investigator's judgment. The maximum permissible treatment suspension is a total of 6 weeks over the duration of the study. Temporary treatment discontinuation and restarting needs to be documented. If temporary discontinuation is due to an AE, it should be reported to the Lilly-designated Medical Monitor.

## 7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (e.g., legal guardian)

- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if the participant enrolls in any other clinical study involving an investigational medicinal product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study, and
- if participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

At the time of discontinuing from the study, if possible, an ET visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the IP and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

### 7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment. Safety follow-up should be performed as outlined in Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events, and Product Complaints) of the protocol.

## 7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

# 8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

## 8.1. Efficacy Assessments

Cognitive and functional testing data will be documented using an eCOA tablet. The audio voice recordings of the rater's questions and the participant's and study partner's responses will also be collected via the eCOA tablet during administration of the cognitive and functional testing for central monitoring of rater scale administration. Cognitive and functional testing for each participant should be performed at approximately the same time on each day, whenever possible, to reduce potential variability.

Note that the CDR should be administered by a different rater than the ADAS-$Cog_{13}$ and MMSE. The ADCS-ADL should be administered by the same rater as the CDR. Each rater should continue administering the same scale whenever possible to the same participant throughout the study. The PI has the responsibility of selecting the raters who will administer the instruments at the site and ensuring all training requirements have been met by those raters. The CDR rater should be blinded to AEs to avoid bias in the CDR assessment.

When administered, cognitive and functional testing should be performed before medical procedures that could be stressful for the participant (e.g., blood draws). Note that some procedures (e.g., MRI, flortaucipir F18 PET imaging) can be conducted on other days within the visit window.

### 8.1.1. Primary Efficacy Assessment

The iADRS (Wessels et al. 2015) represents a composite that was developed using both a theory-driven approach (incorporating measures of both cognition and function) and a data-mining approach (identifying the most sensitive combination of scales through analysis of data from the Alzheimer's Disease Neuroimaging Initiative and the EXPEDITION, EXPEDITION2, and EXPEDITION3 studies).

The iADRS is a simple linear combination of scores from 2 well-established, therapeutically sensitive, widely accepted measures in AD, the ADAS-$Cog_{13}$, and the ADCS-iADL, measuring the core domains of AD. All items of these 2 scales are included without additional weighting of items, yielding face validity and ease of interpretation of the composite relative to its components.

The iADRS score will be derived from the ADAS-Cog$_{13}$ and the ADCS-iADL. The ADAS-Cog$_{13}$ and the ADCS-ADL will be the actual scales administered to participants.

### 8.1.2. Secondary Efficacy Assessments

#### 8.1.2.1. MMSE

The MMSE is a brief instrument used to assess cognitive function in participants (Folstein et al. 1975). The instrument measures orientation, memory, and attention; the ability of the participant to name objects; follow verbal and written commands; write a sentence; and copy figures. The range for the total MMSE score is 0 to 30, with lower scores indicating greater level of impairment.

#### 8.1.2.2. ADAS-Cog$_{13}$

The ADAS-Cog$_{13}$ is a rater-administered instrument that was designed to assess the severity of dysfunction in the cognitive and noncognitive behaviors characteristic of persons with AD (Rosen et al. 1984). The ADAS-Cog$_{13}$ should be administered by the same rater from visit to visit to reduce potential variability.

The cognitive subscale of the ADAS, the ADAS-Cog$_{13}$, consists of 13 items assessing areas of cognitive function that are the most typically impaired in AD: orientation, verbal memory, language, praxis, delayed free recall, digit cancellation, and maze-completion measures (Mohs et al. 1997). The ADAS-Cog$_{13}$ scale ranges from 0 to 85, with higher scores indicating greater disease severity.

#### 8.1.2.3. CDR-Sum of Boxes

The CDR-SB is a semi-structured interview performed with the participant and study partner (informant) that integrates domains of cognition and function into a single overall score (Berg et al. 1992; Morris 1993). By assigning a severity score for each of the 6 domains, and then summating each domain, a total score known as “Sum of Boxes” is obtained. Higher scores indicate greater disease severity.

The CDR global ratings, calculated using an algorithm, range from 0 (no dementia) to 3 (severe dementia) while CDR-SB scores, calculated by adding the box scores, range from 0 to 18 (with higher scores indicative of more impairment). The informant is queried about the participant’s memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The participant’s memory, orientation, judgment, and problem-solving ability are assessed. This scale demonstrates acceptable psychometric characteristics (Coley et al. 2011; Cedarbaum et al. 2013) and has been shown to be sensitive enough to detect disease progression, even in populations with less advanced clinical disease (Williams et al. 2013; Wessels et al. 2015).

The CDR should be administered whenever possible by the same rater from visit to visit to reduce potential variability. The study partner and participant must be interviewed separately. The CDR must always be administered to the study partner first and then to the participant.

#### 8.1.2.4. ADCS-ADL

The ADCS-ADL is a 23-item inventory developed as a rater-administered questionnaire that is to be answered by the participant's study partner (Galasko et al. 1997, 2004). The ADCS-ADL should be administered by the same rater from visit to visit to reduce potential variability.

The ADCS-ADL subset of items (items 6a and 7 to 23) for iADLs will be used as a secondary efficacy measure. The focus in the early symptomatic AD population is on the iADLs rather than the bADLs, which are thought to be affected in more severe stages of the disease. The range for the iADL score is 0 to 59, with lower scores indicating greater disease severity.

For each of the specific items, the study partner is first asked if the participant attempted the ADL during the past 4 weeks. If the participant did attempt the ADL, the study partner is asked to rate the participant's performance level based on a set of performance descriptions. Scores for each item and the overall score for the tool are calculated. The range for the total ADCS-ADL score is 0 to 78, with lower scores indicating greater level of impairment. Separate scores for the bADLs (0 to 19) will also be computed.

### 8.1.3. Exploratory Assessments

#### 8.1.3.1. Digital Clock Drawing Test

The traditional Clock Drawing Test is a well-established and widely used pen and paper cognitive assessment in which individuals draw the face of a clock showing a specific time on a blank page, then copy a pre-drawn clock. The Digital Clock Drawing Test revises this familiar test by combining digitizing pen technology with novel software to precisely measure nuances in cognitive performance beyond task completion (Souillard-Mandar et al. 2016).

Thus, the innovation offered by this technology is the examination of detailed temporal cognitive processes obtained in real time that cannot be captured using the traditional pen and paper testing format.

#### 8.1.3.2. Digit Symbol Substitution Test

The Digit Symbol-Coding test from the Wechsler Adult Intelligence Scale-IV (Wechsler et al. 2008) engages multiple cognitive abilities, but most notably processing speed. The Digit Symbol-Coding is a paper and pencil test presented on a single sheet of paper that requires a participant to match symbols to numbers according to a key located on the top of the page. The participant copies the symbol into spaces below a row of numbers. The number of correct symbols within the allotted time (120 s) constitutes the score. Maximum coding total raw score is 135 points.

## 8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

### 8.2.1. Physical Examinations

Physical examinations will be performed as indicated in the SoA (Section 1.3).

The complete physical examination will include assessment of

- general appearance
- skin, head, eyes, and neck
- lymph nodes
- thyroid
- abdomen (bowel sounds, liver, and spleen palpation)
- back (costovertebral angle tenderness), and
- musculoskeletal, cardiovascular, and respiratory systems.

Neurological examinations will be performed as indicated in the SoA (Section 1.3).

The examinations will include a thorough assessment of

- gait
- balance
- coordination
- cranial nerves
- sensory and motor systems, and
- reflexes.

If necessary, given the training of the PI, a neurologist may be consulted in the event of significant new findings.

If a clinically meaningful change in an MRI is noted during the study, an additional full neurological exam should be performed as soon as possible, along with any other medical follow-up deemed necessary by the investigator.

### 8.2.2. Vital Signs

Vital signs, including temperature, will be measured at visits indicated in the SoA (Section 1.3). Vital signs may be repeated as needed.

#### 8.2.2.1. Blood Pressure

Sitting blood pressure and pulse will be measured after approximately 5 min in the sitting position only, as indicated in the SoA. In addition, orthostatic blood pressure and pulse will be measured supine and standing at designated visits, as detailed in the SoA (Section 1.3).

For orthostatic blood pressure monitoring, participants should be supine for at least 5 min and then stand for at least 3 min prior to taking the respective measurements. If the participant feels unable to stand, only supine vital signs will be recorded.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms.

#### 8.2.2.2. Height, Weight, and Body Temperature

Height and body weight will be measured. Measurements should be taken, when possible, with the same scale for all measurements. Body mass index will be calculated from the height and body weight.

Temperature will be recorded using an oral or tympanic (or another acceptable route) thermometer.

Any body weight data entered into the CRF will be used for the overall data analysis.

### 8.2.3. Electrocardiograms

For each participant, 12-lead digital ECGs will be collected during the double-blind period, according to the SoA (Section 1.3). Participants must be supine for approximately 5 to 10 min before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (replicates) than expected at a timepoint is allowed when needed to ensure high-quality records.

Electrocardiograms will initially be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets entry criteria at the relevant visit(s) and for immediate participant management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/QTc, PR, or AV block interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified, the participant will be assessed by the investigator for symptoms (e.g., palpitations, near syncope, syncope) and, in consultation with the sponsor to determine whether the participant can continue in the study. The investigator or qualified designee is responsible for determining if any change in participant management is needed. The investigator or qualified designee must document his/her review of the ECG printed at the time of evaluation.

All digital ECGs will be electronically transmitted to a designated central ECG laboratory. A cardiologist at the central ECG laboratory will then conduct a full overread. A report based on data from this overread will be issued to the investigative site. These data are not routinely reported back to the investigative site. All data from the overreads will be placed in the Lilly database for analytical and study report purposes.

When there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator's (or qualified designee's) interpretation will be used for study entry and immediate participant management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of collection, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

### 8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form. The laboratory reports must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within the follow-up period after last dose of IP should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Lilly-designated Medical Monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA, standard collection requirements and laboratory manual.
- If laboratory values from non-protocol-specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then report the information as an AE.

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

### 8.2.5. Magnetic Resonance Imaging

Magnetic resonance imaging of the brain will be performed according to the SoA (Section 1.3) and as clinically indicated.

This technology will be used to check for evidence of clinically relevant exclusion and safety findings (vMRI will also be used to calculate brain volumes, as noted in Section 9.4.3).

The MRI scans will be reviewed by the investigator or qualified designee for immediate participant management. Any clinically significant findings noted at baseline that result in a diagnosis should be recorded as a preexisting condition or AE. After the MRI scan is read locally, the MRI scans will be sent for analysis to a centralized MRI vendor designated by Lilly. Final MRI eligibility at screening will be based on the centralized MRI read by the vendor, which will be reported to the site.

Specific analyses of the scans, including calculations of brain volumes, will be interpreted by the centralized MRI vendor for data analysis and report writing purposes.

Results of centrally read MRIs regarding participant care/safety will be reported back to sites.

### 8.2.6. Hepatic Safety Monitoring

Close Hepatic Monitoring

Laboratory tests (Section 10.4), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 h to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

| If a participant with *baseline* results of ... | develops the following elevations: |
|---|---|
| ALT or AST <1.5x ULN | ALT or AST ≥3x ULN |
| ALP <1.5x ULN | ALP ≥2x ULN |
| TBL <1.5x ULN | TBL ≥2x ULN (except for participants with Gilbert's syndrome) |
| ALT or AST ≥1.5x ULN | ALT or AST ≥2x baseline |
| ALP ≥1.5x ULN | ALP ≥2x baseline |
| TBL ≥1.5x ULN | TBL ≥2x baseline (except for participants with Gilbert's syndrome) |

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin level; ULN = upper limit of normal.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated Medical Monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (e.g., heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, and history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive Hepatic Evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

| If a participant with baseline results of... | develops the following elevations: |
|---|---|
| ALT or AST <1.5x ULN | ALT or AST ≥3x ULN with hepatic signs/symptoms*, or<br>ALT or AST ≥5x ULN |
| ALP <1.5x ULN | ALP ≥3x ULN |
| TBL <1.5x ULN | TBL ≥2x ULN (except for participants with Gilbert's syndrome) |
| ALT or AST ≥1.5x ULN | ALT or AST ≥2x baseline with hepatic signs/symptoms*, or<br>ALT or AST ≥3x baseline |
| ALP ≥1.5x ULN | ALP ≥2x baseline |
| TBL ≥1.5x ULN | TBL ≥1.5x baseline (except for participants with Gilbert's syndrome) |

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin level; ULN = upper limit of normal.

* Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for Prothrombin time and INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (e.g., ultrasound or computed tomography [CT] scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated Medical Monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

### 8.2.7. Suicidal Ideation and Behavior Risk Monitoring

Participants being treated with LY3372689 should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Consideration should be given to discontinuing the study medication in participants who experience signs of suicidal ideation or behavior, following a risk assessment.

Families and caregivers of participants being treated with LY3372689 should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms *immediately* to the study investigator.

Baseline assessment of suicidal ideation and behavior/intervention emergent suicidal ideation and behavior will be monitored during Study MTAE using C-SSRS.

**C-SSRS**

Columbia Suicide-Severity Rating Scale is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health trial group for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events.

## 8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Appendix 3:

- AEs
- SAEs
- PCs

AEs will be reported by the participant (or, when appropriate, by a caregiver, study partner, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE, and remain responsible for following up on AEs that are serious, considered related to the IP or study procedures, or that caused the participant to discontinue the IP (see Section 7).

### 8.3.1. Timing Period and Frequency for Collecting AE and SAE Information

All SAEs and AEs will be collected from the signing of the ICF through the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of IP but after signing of the ICF will be recorded on the AE CRF.

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to sponsor begins after the participant has signed the ICF and has received IP or PET tracer. However, if an SAE occurs after signing the ICF, but prior to receiving IP or PET tracer, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 h, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 h of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify the sponsor.

#### 8.3.1.1. Adverse Event Monitoring with a Systematic Questionnaire

Nonleading AE collection should occur prior to the collection of the C-SSRS.

If a suicide-related event is discovered during the C-SSRS but was not captured during the nonleading AE collection, sites should not change the AE form.

If an AE is serious or leads to discontinuation, it needs to be included on the AE form and the process for reporting SAEs is followed.

### 8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs, and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

### 8.3.3. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

### 8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an IP under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC if appropriate according to local requirements.

### 8.3.5. Pregnancy

Women of childbearing potential are excluded from Study MTAE. Therefore, pregnancy is not expected to occur. However, if pregnancy does occur, follow the instructions below.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of IP and until 90 days after the last dose of IP received.

If a pregnancy is reported, the investigator should inform the sponsor within 24 h of learning of the pregnancy.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

### 8.3.6. Adverse Events of Special Interest

Specific safety topics of interest for this study include, but are not limited to, the following:

The topics listed above, as well as other topics which may be subsequently determined by the sponsor, will be subject to enhanced surveillance activities. Additionally, the topics above will be analyzed for presentation in the CSR in accordance with the SAP.

### 8.3.7. Complaint Handling

Lilly collects product complaints on investigational medicinal products or investigational devices used in clinical trials in order to ensure the safety of study participants, to monitor quality, and to facilitate process and product improvements.

Study participants will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the investigational medicinal product so that the situation can be assessed.

## 8.4. Treatment of Overdose

In the event of an overdose, the investigator or treating physician should:

1. Contact the Lilly-designated Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE, laboratory abnormalities, or ECG abnormalities.
3. Obtain a plasma sample for PK analysis of IP if requested by the Lilly-designated Medical Monitor (determined on a case-by-case basis)].

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Lilly-designated medical monitor based on the clinical evaluation of the participant.

## 8.5. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine the plasma concentrations of LY3372689. A maximum of 3 blood samples per participant may be drawn at additional time points during the study, if warranted and agreed upon between both the investigator and sponsor. The actual date and time (24-h clock time) of each sample collected will be recorded. When a blood sample is collected at the time and date of last dose, and next to last dose administration (except at the initial dosing Visit 2), prior to blood sampling should be recorded. Instructions for the collection and handling of blood samples will be provided by the sponsor.

A validated assay will be used to determine plasma LY3372689 concentrations from the blood samples collected. The blood samples will be analyzed at a laboratory approved by the sponsor. The samples will be retained for a maximum of 1 year following last study visit for the study. During this time, any samples remaining after the bioanalysis is complete may be used for exploratory analyses, such as metabolism, protein binding, or bioanalytical method development/validation work. It is intended that blood samples collected from participants who have received placebo will not be analyzed to measure plasma concentrations of LY3372689.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

## 8.6. Pharmacodynamics

**Biomarker Measures**

### 8.6.1. Imaging Measures

**Flortaucipir F18 PET Scan**

Change in the brain tau burden (as assessed by flortaucipir F18 PET) will be compared in LY3372689 and placebo-treated participants for those participants who undergo baseline and follow-up flortaucipir F18 scans as described in the SoA (Section 1.3). Flortaucipir F18 PET provides quantitative assessment of aggregated tau deposition in the brain and can serve as a PD biomarker of accumulation of tau deposits as AD progresses.

**Volumetric MRI**

Assessment of vMRI of the brain will be performed according to the SoA (Section 1.3). LY3372689 and placebo-treatment effects on MRI will be assessed and compared to evaluate the loss of brain volume that occurs in AD participants.

### 8.6.2. Fluid Measures

Plasma P-tau will be measured according to the SoA (Section 1.3). P-tau levels are associated with AD pathology, neurodegeneration, and cognitive worsening (Janelidze et al. 2020, Mattsson-Carlgren et al. 2020, Palmqvist 2020, Thijssen et al. 2020). The P-tau immunoassay is manufactured by Lilly and performed at a central laboratory. When used as a screening test, it is an investigational in vitro diagnostic and will serve to identify participants with increased likelihood of having AD tau pathology. It may not be available to all trial sites for screening purposes, in which case, screening samples from these sites will only be used for exploratory analyses. At study sites utilizing plasma P-tau for screening purposes, participants that meet P-tau study eligibility criteria will have subsequent confirmation of brain tau pathology by flortaucipir F18 PET.

#### 8.6.2.1. Exploratory Biomarkers

Exploratory biomarker samples will be collected at timepoints described in the SoA (Section 1.3) to assess AD pathology, evidence of neurodegeneration and neuroinflammation, as well as to potentially assess additional novel and developing biomarkers of disease state, progression, and association with study treatment. For example, within the study at baseline and post baseline visits, plasma P-tau levels may serve as a disease relevant PD biomarker. Additionally, plasma neurofilament light chain (NFL) levels are believed to reflect neuronal damage and potentially serve as a pharmacodynamic marker for ongoing neurodegeneration in AD. Glial fibrillary acidic protein (GFAP) is a marker of astroglial injury associated with neuroinflammatory changes in the CNS. For these reasons, biomarkers may be tested from exploratory samples and compared in LY3372689 and placebo-treated participants. These may include but are not limited to P-tau217, NFL, and GFAP.

Final testing and analysis plan to be at sponsor discretion.

## 8.7. Genetics

A blood sample for DNA isolation will be collected from participants at screening.

See Appendix 10.7 for information regarding genetic research and Appendix 10.1.12 for details about sample retention and custody.

### 8.7.1. Apolipoprotein E Genotyping

ApoE genotyping is a mandatory part of this study, unless country-specific laws and regulations prohibit this type of testing. Blood sampling for ApoE genotyping will be performed as shown in the SoA (Section 1.3). Neither participants nor investigators will receive the genotype results unless there is a country-specific law or regulation that requires notification of the results.

Failure to collect samples for ApoE will not be considered a protocol deviation if country-specific regulations prohibit the testing of genetic material or transportation of such material outside of the country.

### 8.7.2. Whole Blood Samples for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to LY3372689 and to investigate genetic variants thought to play a role in AD or other neurological conditions. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last study visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3372689 or after LY3372689 becomes commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome-wide association studies, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

## 8.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid, RNA, proteins, lipids, and other cellular elements.

### 8.8.1. Blood Sample Collection for Exploratory Biomarkers

Serum, plasma, and whole blood RNA samples for biomarker research will be collected at the times specified in the SoA (Section 1.3) where local regulations allow. Additionally, as indicated in Section 8.6.2.1, based on emerging technology, biomarkers may be tested from the exploration biomarker samples collected from participants. These may include but are not limited to P-tau217, NFL, and GFAP.

Samples will be used for research on the drug target, disease process, variable response to LY3372689, pathways associated with AD and other neurodegenerative conditions, mechanism of action of LY3372689, and/or research method or in validating diagnostic tools or assay(s) related to AD or other neurodegenerative conditions.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last study visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3372689 or after LY3372689 becomes commercially available.

## 8.9. Immunogenicity Assessments

Not applicable.

## 8.10. Medical Resource Utilization and Health Economics

Dependence, or the level of assistance required by a participant, has been suggested as a construct for assessing the effect of AD treatment. The process of increasing dependence on others is intended as a complementary measure to existing clinical measures in order to help explain the impact of AD on economic issues such as the risk of institutionalization and caregiver burden (McLaughlin et al. 2010; Spackman et al. 2013).

For this purpose, the ADCS-ADL scale will be used to assess changes in dependence levels in Study MTAE. The ADCS-ADL scores will be used to map individuals into 1 of 6 dependence levels (0 to 5):

- Level 0 – no iADL/bADL impairment
- Level 1 – some supervision needed on isolated iADLs
- Level 2 – supervision on multiple iADLs or loss of at least 1 household activity
- Level 3 – supervision on all types of iADLs or homebound
- Level 4 – supervision on some bADLs, and
- Level 5 – impaired transfer or complete incontinence (Kahle-Wrobleski et al. 2015).

An approach to transforming continuous functional scale scores into discrete levels of dependence was examined previously in a longitudinal observational study, with preliminary results suggesting acceptable validity and progression in dependence level over time (Kahle-Wrobleski et al. 2017). At baseline, 49.6% of those with mild AD dementia were dependence

level 2 and 42.7% were at levels 3 or 4. At 18 months, the proportion of participants at level 2 declined to 31.2% while that at levels 3 and 4, rose to 58.8%.

Analyses will be conducted to examine changes in dependence levels across the trial population as well as potential differences on dependence level by treatment group assignment.

# 9. Statistical Considerations

The study population includes early symptomatic AD participants with evidence of elevated pathological tau. The primary efficacy objective of Study MTAE is to demonstrate that LY3372689 slows cognitive and/or functional decline in AD versus placebo as measured by the iADRS after 76 to 124 weeks in participants with moderate levels of tau pathology at screening. Participants with moderate levels of tau pathology are defined as those who meet tau PET inclusion criteria for evidence of tau pathology consistent with AD (Fleisher et al. 2020), but do not have widespread and high levels of cortical tau pathology. High levels of cortical tau pathology by flortaucipir PET is defined by the top quartile of quantitative standardized uptake value ratios in a population of amyloid positive Alzheimer's patients and cognitively normal older controls (Pontecorvo et al. 2019). It is hypothesized that individuals with high tau pathology, representing a later pathological stage of disease, where aggregated neurofibrillary tau tangles have already spread throughout the brain, may be less likely to benefit from LY3372689. For this reason, the primary objective for this study focuses on a sub-population with moderate levels of tau pathology as defined by tau PET. The high tau sub-population will be included in key secondary analyses. The primary analyses will be conducted by a DPM, and MMRM will be performed as a sensitivity analysis.

## 9.1. Statistical Hypotheses

The null hypothesis for the primary analysis is that there is no difference in disease progression between LY3372689 and placebo as measured by iADRS through the end time point in the moderate tau pathology sub-population. The estimand of the primary analysis is the overall treatment effect of LY3372689 vs placebo as measured by percent slowing of disease progression on iADRS in all randomized participants with early symptomatic AD and moderate cortical tau pathology burden that receive up to 124 weeks of study assessments, regardless of study treatment discontinuation.

## 9.2. Sample Size Determination

Approximately 330 participants will be enrolled and randomized in a 1:1:1 ratio to the 3 treatment arms (placebo and 2 active arms of LY3372689). It is expected that approximately 240 participants (i.e., 75%) will complete the double-blind period 2a 76-week treatment period of the study (approximately 80 per treatment arm). Using a DPM model over the entire 124-week treatment period, this sample size will provide CCI [redacted] CCI [redacted] CCI [redacted] If the active LY3372689 treatment arm progression rate is not different than the placebo treatment arm rate, the probability of passing the efficacy criterion specified above (i.e., false positive) is approximately 2.4% CCI [redacted]

CCI [redacted]. The simulation for the power calculation and sample size determination was carried out in the statistical program R, version 3.6.3.

## 9.3. Populations for Analyses

The following populations are defined:

| Population | Description |
|---|---|
| Entered | All participants who sign the ICF. |
| Enrolled/ITT | All participants assigned to treatment, regardless of whether they take any doses of study treatment, or if they take the correct treatment. Participants will be analyzed according to the treatment group to which they were assigned. |
| Efficacy evaluable | For each assessment, the efficacy evaluable population will be defined as all participants with a baseline measurement and at least 1 complete post-baseline measurement for that respective assessment. Participants will be grouped according to randomized treatment assignment (LY3372689 or placebo), even if the participant does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. |
| Biomarker evaluable | Same population as efficacy evaluable. |
| Safety | All participants randomly assigned to IP and who take at least 1 dose of IP. |
| Pharmacokinetic analysis | Same as safety. |

Abbreviations: ICF = informed consent form; IP = investigational product.

## 9.4. Statistical Analyses

### 9.4.1. General Considerations

Statistical analysis of this study will be the responsibility of the Sponsor or its designee.

Unless otherwise noted, all pairwise tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 (or equivalently, a 1-sided 0.025 alpha level); 2-sided CIs will be displayed with a 95% confidence level. All tests of interactions between treatment and other factors will be conducted at an alpha level of 0.05.

Bretz's graphical approach may be utilized to provide strong control of the study wise Type I error rate for the primary and key secondary hypotheses at an alpha level of 0.05 (Bretz et al. 2009, 2011). Details on the graphical approach and testing strategy will be specified in the SAP.

All efficacy analyses will follow the ITT principle unless otherwise specified. An ITT analysis is an analysis of data by the groups to which participants are assigned by random allocation, even if the participant does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol.

When change from baseline is assessed, participants will be included in the analysis only if both a baseline and a postbaseline measure are available. Unless otherwise defined, a baseline measure is the last non-missing observation collected prior to the first administration of study medications. Endpoint is the last non-missing postbaseline measurement.

For efficacy and biomarker analyses, observations collected at nonscheduled visits will not be included in the analyses unless the nonscheduled visit coincided with a protocol scheduled visit or the nonscheduled visit is within the tolerance window as pre-specified in the SAP. If any of the individual items for ADAS-$Cog_{13}$ or ADCS-ADL or CDR-SB are missing or unknown, every effort will be made to obtain the score for the missing item or items. If either ADAS-$Cog_{13}$ or ADCS-iADL is missing, iADRS score will be considered missing. For all other scales, if any item is missing, any total or sum involving that item will be considered missing. For all scales, if a limited number of individual test items are missing, imputation using prorating will be implemented to obtain a total score. Details of this prorating and the circumstances in which it will be used are included in the SAP.

A database lock is expected to occur after all randomized participants have had a chance to complete their final study visit in the double-blind period of the study (study period 2a/2b). Efficacy and safety analyses will be conducted based on data collected during the double-blind period. Data collected during post-treatment safety follow-up period (study period 3) will be summarized and analyzed separately.

Additional database lock(s) may occur during the post-treatment safety follow-up period (study period 4). Efficacy and safety analyses will be conducted based on data collected during the double-blind and/or post-treatment safety follow-up period.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and the CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The study will include 2 SAPs: a main study SAP (referred to as Study SAP) which will detail the analyses for the objectives for double-blinded, placebo-controlled phase, and post-treatment safety follow-up period; a supplemental SAP which will detail the additional exploratory analyses using data collected from post-treatment safety follow-up period.

The main Study SAP will be finalized prior to unblinding of all participants in the placebo-controlled phase, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAPs, where appropriate.

### 9.4.2. Primary Endpoint(s)

Study MTAE has a 76-week common close design wherein all enrolled participants continue on study drug and complete study assessments until last enrolled participant that has not discontinued reaches 76 weeks of double-blind treatment. The maximum duration of treatment is 124 weeks.

The primary objective of this study is to test the hypothesis that LY3372689 slows cognitive and functional decline in early symptomatic AD participants with moderate cortical tau burden as measured by iADRS compared with placebo through end time point (76-124 weeks). This will be assessed using DPM as the primary analysis, and MMRM analysis will be performed as a sensitivity analysis.

The iADRS score at each scheduled postbaseline visit (according to the SoA) during the treatment period will be the dependent variable. The DPM is as follows:

$$Y_{ij} = \gamma_i + e^{\theta_{T_i}} \sum_{v=0}^{j} \alpha_v + \varepsilon_{ij}, i = 1, 2, \ldots k; j = 1, 2, \ldots l$$

where $Y_{ij}$ denotes the clinical outcome at visit $j$ for participant $i$, clinical outcome scores at baseline (prior to treatment) is $Y_{i0}$. $T_i$ denotes the treatment arm for participant i. The parameter $\gamma_i$ ($i$=1, 2, …, $k$) represents the subject-specific random effect for participant i. $e^{\theta_T}$ is the disease progression ratio (DPR) for treatment $T$ and $e^{\theta_T} = 1$ for placebo; $e^{\theta_1}$ and $e^{\theta_2}$ represent the DPR of the low dose and the high dose, respectively. The parameter $\alpha_v$ is the mean change of placebo response from visit $v$-1 to $v$. $\varepsilon_{ij}$ is the error term. Any stratification variables used for randomization such as investigator site and prior or current use of any approved disease-modifying therapy for AD will be included in the model. Baseline score, baseline age, concomitant acetylcholinesterase inhibitor (AChEI)/memantine use (yes/no) will be included in the model as well. Diffuse priors will be used for the Bayesian inferences in the DPM analysis. A DPR less than 1 corresponds to a slowing of disease progression; similarly, a DPR greater than 1 reflects some evidence of cognitive worsening. The DPM will be fitted to the data and Bayesian inferences will be summarized including posterior distribution of DPR and posterior probabilities of various DPR thresholds of interest (e.g., 0.75 which translates to 25% slowing of disease progression with LY3372689 group versus placebo). The null hypothesis is that the DPR between the LY3372689 group versus placebo equals 1.

The primary endpoint will also be assessed using natural cubic spline model with degrees of freedom 2 (NCS2) and MMRM to serve as sensitivity analyses. Additional models/analyses may be considered if deemed appropriate. The SAP will describe the planned analyses in greater details.

### 9.4.3. Secondary Endpoint(s)

The key secondary objective of this study is to test the hypothesis that LY3372689 slows cognitive and functional decline in early symptomatic AD participants in the overall population as measured by iADRS compared with placebo through end time point (76-124 weeks). It will be analyzed using the NCS2, MMRM and the Bayesian DPM as described in Section 9.4.2, with the adjustment for tau burden (moderate versus high) as defined by flortaucipir PET.

Other secondary efficacy outcomes include ADAS-$Cog_{13}$, ADCS-iADL, CDR-SB, and MMSE. Each of these 4 secondary efficacy endpoints will be assessed using the same analysis method(s) applied to the primary endpoint iADRS and will be analyzed for both moderate tau sub-population and the overall population. The change from baseline score at each scheduled

postbaseline visit (according to the SoA) during the treatment period will be analyzed using the NCS2. Greater details of model specifications will be provided in the SAP.

The change from baseline to Week 76 in tau deposition (as measured by flortaucipir F18 PET scan) will be analyzed using an ANCOVA model with terms of baseline value and treatment.

Longitudinal change in vMRI parameters up to Week 76 will be analyzed using MMRM including the following terms in the model: treatment, visit, treatment-by-visit interaction, baseline vMRI, and intracranial volume. Other baseline covariates may be included.

For data beyond Week 76, including flortaucipir F18 PET and MRI, MMRM may be used to analyze the data with terms of baseline value and treatment.

An additional analyses of secondary efficacy and biomarkers endpoints may be performed and will be pre-specified in the SAP.

### 9.4.4. Tertiary/Exploratory Endpoint(s)

Exploratory endpoints and their respective analyses will be described in the SAP.

### 9.4.5. Treatment Group Comparability

#### 9.4.5.1. Participant Disposition

All participants who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

The reasons for discontinuation will be collected when the participant's participation in the study ends and will be summarized by treatment group for all randomized participants. The percentage of participants discontinuing from each treatment group will be compared between groups using Fisher's exact test. The comparisons will be done for the overall percentage of participants who discontinue and for select specific reasons for discontinuation.

#### 9.4.5.2. Participant Characteristics

The participant's age, sex, race, height, body weight, body mass index (weight (kg)/[height (m)]$^2$), tobacco use, alcohol use, caffeine use, years of education, work status, marital status, time since onset of first AD symptoms, time since diagnosis, baseline MMSE, ApoE genotype (e.g., E4 carrier versus non-carrier), having 1 or more first degree relatives with AD, and use of approved prescription AD medications will be recorded.

Baseline characteristics will be summarized by treatment group, primary efficacy subpopulation, and overall population. Summaries will include descriptive statistics for continuous and categorical measures. Fisher's exact test or Pearson's chi-square test will be used for treatment-group comparisons of categorical data. For continuous data, analysis of variance (ANOVA), with independent factors for treatment and investigator, will be used.

#### 9.4.5.3. Prior and Concomitant Therapy

Prior medications are defined as those that stop before randomization (Visit 2). Concomitant medications are defined as those being taken on or after randomization (Visit 2). A summary of

concomitant medications will be presented as frequencies and percentages for each treatment group. Fisher's exact test will be used to test for treatment differences between groups.

If the start or stop dates of therapies are missing or partial to the degree that determination cannot be made of whether the therapy is prior or concomitant, the therapy will be deemed concomitant.

Prior and concomitant medications will be listed.

Summary tables will also be provided for concomitant anticholinergics that affect cognitive function and use of approved prescription AD medications.

Medications will be coded using the World Health Organization drug dictionary.

#### 9.4.5.4. Treatment Compliance

The proportion of participants who are significantly noncompliant as described in Section 6.4 of this protocol will be summarized and compared among all treatment groups using Fisher's exact test.

### 9.4.6. Safety Analyses(s)

All safety analyses will be made on the Safety Population. Refer to the SAP for additional details.

### 9.4.7. Other Analyses

#### 9.4.7.1. Pharmacokinetic/Pharmacodynamic Analyses

LY3372689 plasma concentrations will be illustrated graphically and summarized descriptively.

If warranted and based on availability of data, the exposure-response relationship of LY3372689 concentrations to biomarkers, pharmacodynamic endpoints, efficacy endpoints, and/or safety endpoints may be explored. Data from other clinical studies evaluating LY3372689 may be combined with data from this study to support exposure-response analyses. Such analyses may be reported separately.

#### 9.4.7.2. Analysis of C-SSRS Data

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide (CUIMC 2016).

## 9.5. Interim Analyses

Interim analyses may be conducted for Study MTAE; for example, when 50% of randomized participants have had a chance to complete 52 weeks of treatment (Visit 15), data may be used to evaluate whether to stop the study for futility. Operational details and a quantitative framework to provide information for these decisions will be documented in the SAP.

Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results only if they need to know for the safety of trial participants.

Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

The timing of dissemination of data summaries based on interim analyses is addressed in Section 10.1.6.

## 9.6. Data Monitoring Committee

For details on DMC, refer to Appendix 10.1.5

# 10. Supporting Documentation and Operational Considerations

## 10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - applicable ICH GCP Guidelines,
    - regulation (EU) No. 536/2014, if applicable, and
    - other applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures,
    - providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
    - reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.
- Investigator sites are compensated for participation in the study as detailed in the CTA.

### 10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial

certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

### 10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

Participants who are rescreened are required to sign a new ICF.

### 10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his/her data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.
- The participant must be informed through the informed consent by the site personnel that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.
- The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

### 10.1.5. Committees Structure

A DMC consisting of members external to Lilly will be established. The purpose of the DMC is to conduct periodic monitoring of clinical trial data for Study MTAE. The DMC will consist of a minimum of 3 members, including a physician with expertise in AD and a statistician.

No member of the DMC will have contact with study sites. An SAC will prepare and provide unblinded data to the DMC. The SAC members will be from a TPO designated by Lilly. The SAC members will be external to the study team and will have no contact with sites and no privileges to influence changes to the ongoing studies. The timing and frequency of the periodic clinical trial data review by the DMC will be detailed in a DMC charter.

The DMC is authorized to separately evaluate unblinded interim efficacy and safety analyses. In addition, the DMC may request key efficacy data to put safety observations into context and to assess a reasonable benefit/risk profile for ongoing participants in the study. The DMC will make recommendation to the Lilly Research Laboratories Senior Management Designee, who may order the immediate implementation of the DMC recommendation, or may convene an internal review committee, which is independent from the study team, to review the recommendation according to standard Lilly policy. Study sites will receive information about interim results ONLY if it is required for the safety of their participants.

### 10.1.6. Dissemination of Clinical Study Data

**Reports**

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

**Data**

The sponsor provides access to all individual participant data collected during the trial and after anonymization, with the exception of PK or genetic data. Data are available for request 6 months after the indication studied has been approved in the US and EU, and after primary

publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, SAP, CSR, and blank or annotated CRFs, will be provided in a secure data sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

### 10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. This includes laboratory tests, medical records, and clinical notes.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the sponsor. All completed CRFs must be signed prior to archival.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques, are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- The sponsor or designee will perform monitoring to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

**Data Capture System**

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An (EDC system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, COA data (participant-focused outcome instrument) will be collected by the participant and/or investigator site personnel, via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Additionally, eCOA data (participant-focused outcome instrument) will be directly recorded by the investigator site personnel into an instrument (e.g., tablet). The eCOA data will serve as the source documentation and the investigator does not maintain a separate, written, or electronic record of these data.

Data collected via the sponsor-provided data capture system will be stored at third party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system, and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Sponsor data warehouse.

Data from complaint forms submitted to Sponsor will be encoded and stored in the global product complaint management system.

### 10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

### 10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator, and
- discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and assures appropriate participant therapy and/or follow-up.

### 10.1.10. Publication Policy

In accordance with the sponsor’s publication policy, the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

### 10.1.11. Investigator Information

Physicians with a specialty in neurology, geriatrics, or psychiatry will participate as investigators in this clinical trial. In addition, licensed clinicians who have clearly documented experience in AD may participate as investigators in this clinical study.

### 10.1.12. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3372689 or after LY3372689 become(s) commercially available.

| Sample Type | Custodian | Retention Period after Last Study Visit* |
|---|---|---|
| Exploratory biomarkers | Sponsor or Designee | 15 years |
| PK | Sponsor or Designee | 2 years |
| Genetics | Sponsor or Designee | 15 years |

*Retention periods may differ locally.

## 10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the central laboratory (unless specified otherwise below).
    - Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
    - Additional tests may be performed at any time during the study as determined necessary by the investigator or as required by local regulations.
    - Investigators must document their review of each laboratory safety report.
    - Laboratory analyte results denoted below that could unblind the study will not be reported to investigative sites or other blinded personnel.

| **Clinical Laboratory Tests** | **Comments** |
|---|---|
| **Hematology** | Assayed by Lilly-designated laboratory |
| Hemoglobin | |
| Hematocrit | |
| Erythrocyte count (RBCs) | |
| Mean cell volume | |
| Mean cell hemoglobin | |
| Mean cell hemoglobin concentration | |
| Leukocytes (WBCs) | |
| Differential | |
| Neutrophils, segmented | |
| Lymphocytes | |
| Monocytes | |
| Eosinophils | |
| Basophils | |
| Platelets | |
| **Clinical Chemistry** | Assayed by Lilly-designated laboratory |
| Sodium | |
| Potassium | |
| Total bilirubin | |
| Direct bilirubin | |
| ALP | |
| ALT | |
| AST | |
| GGT | |
| BUN | |
| Creatinine | |
| CK | |
| Uric acid | |
| Albumin | |

| Clinical Laboratory Tests | Comments |
|---|---|
| Calcium | |
| Glucose | |
| Cholesterol | |
| **Hormone Panel** | Assayed by Lilly-designated laboratory |
| FSH | |
| LH | |
| Inhibin B | |
| Testosterone | |
| Estrogen | |
| **Urinalysis** | Assayed by Lilly-designated laboratory |
| Specific gravity | |
| pH | |
| Protein | |
| Glucose | |
| Ketones | |
| Blood | |
| Urine leukocyte esterase | |
| **Biomarkers** | Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. |
| ApoE | Neither participants nor investigators will receive the genotype results unless there is a country-specific law or regulation that requires notification of the results. |
| NFL | |
| GFAP | |
| P-tau217 | |
| **Hepatic Testing** | Assayed by Lilly-designated laboratory |
| HBsAg | |
| Hepatitis C virus RNA PCR | |
| **Genetics sample** | Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. |
| **Stored Samples** | Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. |
| Exploratory biomarker samples: | |
| PaxGene Tube for RNA | |
| Plasma | |
| Serum | |

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; ApoE = apolipoprotein E; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; FSH = follicle-stimulating hormone; GFAP = glial fibrillary acidic protein; GGT = gamma-glutamyl transferase; HBsAg = hepatitis B surface antigen; IgE = immunoglobulin E; LH = luteinizing hormone; NFL = neurofilament light chain; NMH = N-methylhistamine; RBC = red blood cell; PK = pharmacokinetics; P-tau = phosphorylated tau; RNA = ribonucleic acid; WBC = white blood cells.

## 10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### 10.3.1. Definition of AE

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. |

| **Events <u>Meeting</u> the AE Definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, or vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).<br>• Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.<br>• New condition(s) detected or diagnosed after IP administration, even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.<br>• "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE/SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE/SAE if they fulfill the definition of an AE/SAE. |

**Events NOT Meeting the AE Definition**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### 10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE, even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

**An SAE is defined as any untoward medical occurrence that at any dose:**

**a. Results in death**

**b. Is life-threatening**

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

**c. Requires in participant hospitalization or prolongation of existing hospitalization**

- In general, hospitalization signifies that the participant has been admitted to the hospital for observation and/or treatment that would not have been appropriate in the physician's office or out participant setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

**d. Results in persistent disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

**f. Other situations:**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

**g.** Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

### 10.3.3. Definition of Product Complaints

**Product Complaint**

- A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:
  - Deficiencies in labeling information.
- Product complaints related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.
- Device deficiencies are product complaints.

### 10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

**AE, SAE, and Product Complaint Recording**

- When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

- The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate (e)CRF page, and product complaint information is reported on the Product Complaint Form.

Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the (e)CRF page for AE/SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

**Assessment of Causality**

- The investigator is obligated to assess the relationship between IP and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IP administration will be considered and investigated.

- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-Up of AEs and SAEs**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings, including histopathology.

### 10.3.5. Reporting of SAEs

**SAE Reporting via an Electronic Data Collection Tool**

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 h.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Lilly-designated medical monitor by telephone.
- SAE reporting is done through the eCRF.

**SAE Reporting via Paper CRF**

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Lilly-designated Medical Monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found on the paper CRF.

### 10.3.6. Regulatory Reporting Requirements

**SAE Regulatory Reporting**

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

**EU-specific regulatory reporting requirements**

The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to EU regulatory requirements. The sponsor will comply with applicable regulatory requirements relating to safety reporting to the regulatory authority, per European Union Clinical Trial Regulation 536/2014 submission of SUSARs to the EudraVigilance database.

## 10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-Up Assessments

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with participants in consultation with the Lilly, or its designee, CRP.

**Hepatic Evaluation Testing**

See Section 8.2.6 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed in addition to central testing when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

| **Hematology** | **Clinical Chemistry** |
|---|---|
| Hemoglobin | Total bilirubin |
| Hematocrit | Direct bilirubin |
| Erythrocytes (RBCs) | ALP |
| Leukocytes (WBCs) | ALT |
| Differential: | AST |
| Neutrophils, segmented | GGT |
| Lymphocytes | CK |
| Monocytes | **Other Chemistry** |
| Basophils | Acetaminophen |
| Eosinophils | Acetaminophen protein adducts |
| Platelets | Alkaline phosphatase isoenzymes |
| Cell morphology (RBC and WBC) | Ceruloplasmin |
| | Copper |
| **Coagulation** | EtOH |
| Prothrombin time, INR (PT-INR) | Haptoglobin |
| **Serology** | Immunoglobulin IgA (quantitative) |
| HAV testing: | Immunoglobulin IgG (quantitative) |
| HAV total antibody | Immunoglobulin IgM (quantitative) |
| HAV IgM antibody | PEth |
| HBV testing: | **Urine Chemistry** |
| HBsAg | Drug screen |
| anti-HBs | EtG |
| anti-HBc | **Other Serology** |

| | |
|---|---|
| Hepatitis B core IgM antibody | ANA |
| Hepatitis B core IgG antibody | ASMA [a] |
| HBV DNA [d] | Anti-actin antibody [b] |
| HCV testing: | EBV testing: |
| HCV antibody | EBV antibody |
| HCV RNA [d] | EBV DNA [d] |
| HDV testing: | CMV testing: |
| HDV antibody | CMV antibody |
| HEV testing: | CMV DNA [d] |
| HEV IgG antibody | HSV testing: |
| HEV IgM antibody | HSV (Type 1 and 2) antibody |
| HEV RNA [d] | HSV (Type 1 and 2) DNA [d] |
| **Microbiology [c]** | LKM-1 antibody |
| Culture: | |
| Blood | |
| Urine | |

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANA = anti-nuclear antibody; anti-HBc = hepatitis B core total antibody; anti-HBs = hepatitis B surface antibody; ASMA = anti-smooth muscle antibody; AST = aspartate aminotransferase; CK = creatine kinase; CMV = cytomegalovirus; EBV = Epstein-Barr virus; EtG = ethyl glucuronide; EtOH = ethyl alcohol; GGT = gamma-glutamyl transferase; HAV = hepatitis A virus; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HEV = hepatitis E virus; HSV = herpes simplex virus; LKM-1 = liver kidney microsomal type 1, Peth = phosphatidylethanol; RBC = red blood cell; WBC = white blood cell

Footnotes:

[a] Not required if anti-actin antibody is tested.

[b] Not required if anti-smooth muscle antibody (ASMA) is tested.

[c] Assayed ONLY by investigator-designated local laboratory; no central testing available.

[d] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

## 10.5. Appendix 5: Flortaucipir F18 Tau PET Imaging

Flortaucipir F18 PET scans will be performed as part of the study eligibility criteria and as indicated in the SoA (Section 1.3).

For inclusion and exclusion criteria related to the flortaucipir F18 PET scans, refer to Sections 5.1 and 5.2.

Site investigators, participants, and study partners will only be informed of the eligibility results of PET scans obtained prior to randomization, as they relate to the study, and will not be informed of scan results obtained post-randomization. Any significant findings that may be of potential medical concern will be provided for appropriate follow-up.

**PET Scan-Specific Information**

**PET Scan Procedures**

Specific imaging acquisition protocols designed to ensure consistency across sites will be provided in a PET Imaging Manual.

**Scan Safety**

The primary risk related to flortaucipir F18 PET is radiation exposure. Details on the amount of exposure estimated to occur on each imaging occasion and cumulatively are shown in the table below and will be provided. Details on the clinical information to date regarding flortaucipir F18 exposure will be provided in the ICF. More detailed information about the known and expected benefits and risks of flortaucipir F18 can be found in the IB.

Participants must minimize movement during each PET procedure, which can last approximately 30 min for each scan. Most state-of-the-art imaging systems are designed to reduce head motion and participant discomfort.

The table below shows the effective radiation dose of the Study MTAE's PET scans.

| | Effective Dose (mSv) per Scan[a,b] | Number of Scans in First Year | Effective Dose (mSv) for Scans in First Year | Number of Scans in Second Year[a] | Effective Dose (mSv) for Scans in Second Year | Sum of Effective Dose (mSv) for Years 1 and 2 |
|---|---|---|---|---|---|---|
| Flortaucipir F18 Scan (10 mCi IV) | 9.10 | 1 | 9.10 | 2 | 18.20 | 27.30 |

Abbreviations: IV = intravenous infusion; PET = positron emission tomography.

[a] All participant will receive at least one scan in second year, a second scan in Year 2 will occur for those who will reach Week 100 in Period 2b.

[b] Dose shown includes radiation exposure from the radiotracer and assumes a nonclinical CT scan is obtained (estimated at 0.4 mSv) as part of the PET scan attenuation correction process when the scan is done on a PET/CT scanner. A clinical CT scan is not needed during the PET scan session and, because it will add additional radiation exposure, it is not recommended.

Note: In the event a repeat scan is required (e.g., the scan is not analyzable), 1 additional flortaucipir F18 scan may be received in 1 year.

## 10.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Please see Section 5.1 for details on contraceptive guidance.

**Collection of Pregnancy Information**

**Male participants with partners who become pregnant**

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 h of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

**Female Participants who become pregnant**

Women of childbearing potential are excluded from Study MTAE. Therefore, pregnancy is not expected to occur. However, if a female participant becomes pregnant:

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 h of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant, and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at >20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

## 10.7. Appendix 7: Genetics

**Use/Analysis of DNA**

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood/saliva sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to study intervention or indication and related diseases. They may also be used to develop tests/assays including diagnostic tests related to study intervention and/or interventions of this drug class and indication. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed for planned analyses. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study intervention or study interventions of this class or indication continues but no longer than 15 years or other period as per local requirements.

## 10.8. Appendix 8. Provisions for Changes in Study Conduct During Exceptional Circumstances

**Implementation of this Appendix**

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

**Exceptional Circumstances**

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

**Implementing Changes under Exceptional Circumstances**

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies, and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific conditions in which notification is required. To protect the safety of study participants, urgent changes may be implemented before approval but need to be reported as soon as possible. All approvals must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

**Considerations for Making a Change**

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with GCP, enabling participants to continue safely in the study and maintaining the integrity of the study.

**Informed Consent**

Additional consent from the participant will be obtained, if required, for:

- participation in remote visits, as defined in Section "Remote Visits"
- dispensation of additional study intervention during an extended treatment period
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

**Changes in Study Conduct during Exceptional Circumstances**

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

Visits referenced below are indicative of visits that are not otherwise indicated in the SoA as televisits or remote visits. These changes are for additional televisits and remote visits under exceptional circumstances.

The following changes in study conduct will not be considered protocol deviations.

**Remote Visits**

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged. Furthermore, every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

**Telemedicine:** Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner may include the assessments below.

Clinician-Administered Assessments (Electronic)

- ADAS-$Cog_{13}$
- ADCS-ADL
- CDR
- MMSE
- DSST, and
- Digital Clock.

Clinician-Administered Assessment (Paper)

- C-SSRS baseline
- C-SSRS Since Last Visit

**Mobile healthcare:** Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include, but are not limited to,

- Physical Evaluation
- Laboratory Tests, and
- Sample Collections.

**Other alternative locations:** Procedures that may be done at an alternate location, other than listed above include

- Physical Evaluation
- Laboratory Tests, and
- Sample Collections.

**Local Laboratory Testing Option**

Local laboratory testing may be conducted in lieu of some central laboratory testing.

- Obtain local labs for safety (hematology, chemistry, hormone panel, and urinalysis) when applicable, as per the SoA.
- All labs will be reviewed by the investigators. Lilly Medical should be informed of any labs that meet criteria for temporary or permanent study drug discontinuation.
- Sign and date review of local labs per normal process and follow-up with the participant as needed. Results will not be recorded in the eCRF.
- Safety labs should be obtained as specified in the SoA.

The local laboratory must be qualified in accordance with applicable local regulations.

**Study Intervention and Ancillary Supplies**

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf, and
- arranging delivery of study supplies.

These requirements must be met before action is taken:

- Alternate delivery of IP should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (e.g., participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (i.e., storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

**Screening Period Guidance**

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening visit are valid for a maximum of 90 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If paused for less than 90 days from screening, the participant will proceed to the next study visit per the usual SoA, provided that randomization visit must be conducted within 90 days from first screening
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.

  - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.

- If paused for more than 90 days from screening: the participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. This screen fail is allowed in addition to the main protocol screen fail. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual SoA should be followed, starting at screening visit to ensure participant eligibility by randomization visit.

**Adjustments to Visit Windows**

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.
This table describes the allowed adjustments to visit windows.

| Visit Number | Tolerance |
|---|---|
| For Study Periods 2a and 2b | ±14 days from intended visit date for all visits. |

For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

**Documentation**

Changes to study conduct will be documented:

- Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.
- Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

## 10.9. Appendix 9: Abbreviations

| Term | Definition |
|---|---|
| **abuse** | Use of a study intervention for recreational purposes or to maintain an addiction or dependence |
| **ADAS-Cog$_{13}$** | Alzheimer's Disease Assessment Scale - Cognitive subscale |
| **ADCS-ADL** | Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory |
| **ADCS-iADL** | Alzheimer's Disease Cooperative Study - instrumental Activities of Daily Living |
| **AE** | adverse event |
| **ALP** | alkaline phosphatase |
| **ALT** | alanine aminotransferase |
| **ANCOVA** | analysis of covariance |
| **ApoE** | apolipoprotein E |
| **AST** | aspartate aminotransferase |
| **authorized IMP** | *Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product |
| **bADLs** | basic Activities of Daily Living |
| **blinding/masking** | a single-blind study is one in which the investigator and/or his staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the participant are not.<br>A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received. |
| **MMRM** | Mixed model for repeated measures |
| **CDR-SB** | Clinical Dementia Rating Scale - Sum of Boxes |
| **CIOMS** | Council for International Organizations of Medical Sciences |
| **CNS** | central nervous system |
| **COA** | clinical outcome assessment |
| **complaint** | a complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system. |
| **compliance** | adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements. |

| Term | Definition |
|---|---|
| **CRP** | clinical research physician: individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer. |
| **CSR** | clinical study report |
| **CTA** | clinical trial agreement |
| CCI | [redacted] |
| **DART** | Developmental and Reproductive Toxicology |
| **DMC** | Data Monitoring Committee |
| **DPM** | disease progression model |
| **ECG** | electrocardiogram |
| **eCOA** | electronic Clinical Outcome Assessment |
| **EDC** | electronic data capture |
| **enroll** | the act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment. |
| **enter** | participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives. |
| **EO** | enzyme occupancy |
| **GCP** | good clinical practice |
| **HBsAg** | Hepatitis B surface antigen |
| **iADRS** | integrated Alzheimer's Disease Rating Scale |
| **IB** | Investigator's Brochure |
| **ICF** | Informed Consent Form |
| **ICE** | Independent Ethics Committees |
| **ICH** | International Council for Harmonisation |
| **INR** | international normalized ratio |
| **IMP** | Investigational Medicinal Product (see also "investigational product")<br>A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial. |

| Term | Definition |
|---|---|
| **Informed consent** | a process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form. |
| **interim analysis** | an interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked. |
| **investigational product** | a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP." |
| **IP** | investigational product |
| **IRB** | Institutional Review Boards |
| **ITT** | intention to treat: the principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment. |
| **IWRS** | interactive web-response system |
| **MAD** | multiple ascending dose |
| **medication error** | Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time.<br>In addition to the core five rights, the following may also represent medication errors:<br>• dose omission associated with an AE or a product complaint<br>• dispensing or use of expired medication<br>• use of medication past the recommended in-use date<br>• dispensing or use of an improperly stored medication<br>• use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or<br>• shared use of cartridges, prefilled pens, or both. |
| **misuse** | Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription |
| **MMSE** | Mini Mental State Examination |

| Term | Definition |
|---|---|
| **NFL** | neurofilament light chain |
| **NIMP** | non-investigational medicinal product |
| **NOAEL** | no-observed-adverse-effect level |
| **OGA** | O-linked N-acetyl glucosaminidase |
| **O-GlcNAc** | O-linked β-N-acetyl glucosamine |
| **OLE** | open-label extension |
| **participant** | equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control |
| **PC** | product complaint |
| **PET** | Positron emission tomography |
| **PK/PD** | pharmacokinetics/pharmacodynamics |
| **PPS** | per-protocol set: The set of data generated by the subset of participant who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model. |
| **PRO/ePRO** | participant-reported outcomes/electronic participant-reported outcomes |
| **QD** | once daily |
| **QTc** | corrected QT interval |
| **SAC** | statistical analysis center |
| **SAD** | single ascending dose |
| **SAE** | serious adverse event |
| **SAP** | statistical analysis plan |
| **screen** | the act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. |
| **SoA** | schedule of activities |
| **SUSARs** | suspected unexpected serious adverse reactions<br>Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study intervention. |
| **TBL** | total bilirubin level |

| Term | Definition |
|---|---|
| **TPO** | third-party organization |
| **TEAE** | treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment. |
| **ULN** | upper limit of normal |
| **vMRI** | volumetric magnetic resonance imaging |

## 10.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

### Amendment [d] (18-Apr-2024)

This amendment is considered to be nonsubstantial.

### Overall Rationale for the Amendment

The main rationale for this amendment is to make corrections as specified in the table below.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.1 Study Intervention(s) Administered | Deleted sentence about supplying blister packaging. | To provide flexibility in the packaging to be used. |
| 6.3 Measures to Minimize Bias: Randomization and Blinding | Deleted sentence about supplying blister packaging. | To provide flexibility in the packaging to be used. |
| 7.3 Lost to Follow-Up | Deleted Note about operations for lost to follow-up. | To provide flexibility in operations. |

### Amendment [c] (22-Mar-2024)

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the

- safety or the rights of the study participants, and
- reliability and robustness of the data generated in the clinical study.

### Overall Rationale for the Amendment:

The main rationale of this amendment is to update the study design with the addition of an optional open-label extension period and an optional substudy for flortaucipir F18 PET imaging and MRI scans to assess long term safety and extended biomarker.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Throughout | Revised flortaucipir PET at all instances to reflect:<br>flortaucipir F18 PET | For consistency and clarity |
| Title Page | Regulatory Agency Identifier Number(s):<br>Added EU CT number | Compliance with EU-CTR |
| | Added subsections: | |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1. Synopsis | • Regulatory Agency Identifier Numbers (IND, EudraCT, and EU CT number)<br>• Study Population<br>• Ethical Considerations of Benefit/Risk | |
| | Deleted language from Rationale | For conciseness |
| | Objectives and Endpoints subsection:<br>Deleted exploratory objectives and endpoint<br>Added table and corresponding abbreviations depicting the objectives and endpoints for the open-label extension (OLE) period | For conciseness<br><br>To reflect the changes in the modified open-label study design |
| | Overall design subsection:<br>Updated the overall design as per the modified study design and deleted the disclosure statement. | |
| | Intervention Groups and Duration subsection:<br>• Modified total study duration from "137 weeks" to "217 weeks"<br>• Added duration and follow-up for the OLE period | |
| 1.2. Schema | New figure and corresponding footnote have been added for the OLE period | To reflect the changes in the modified open-label study design |
| 1.3. Schedule of Activities (SoA)<br>1.3.1. Study Period 2a-Treatment Period<br>1.3.2. Study Period 2b-Treatment Period | Added table headings | Clarification |
| 1.3.1. Study Period 2a-Treatment Period | Laboratory tests and sample collection row:<br>Added hormone panel testing (testosterone, LH, FSH, Inhibin B) at Visit 21 | CCI [redacted] |
| | • Added footnote 'c' detailing specifics for ET MRI scan<br>• Updated footnote 'h' with specifics for hormone panel collection | Clarification |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2. Study Period 2b-Treatment Period | Laboratory tests and sample collection row:<br>• Added hormone panel testing (testosterone, LH, FSH, Inhibin B) at Visit 23, 25, 27, 29, ET, V801 and added applicable comments<br>• Added footnote 'd' and 'i' detailing specifics for ET MRI scan and hormone panel collection | CCI [redacted] |
| 1.3.3. Study Period 4-Open-Label Extension Period (newly added section) | Added study activities and procedures to be performed in the OLE period. Also, added corresponding footnote | To reflect the changes in the modified open-label study design |
| 3. Objectives and Endpoints | Added objectives and endpoints to be evaluated in the OLE period | |
| 4.1. Overall Design | • Modified total study duration<br>• Added duration and follow-up for the OLE period<br>• Added criteria for participants who will be offered to enter OLE Study MTAE | |
| 4.1.5. Optional Extension Period (newly added section) | Added eligibility criteria, dosing, and follow-up duration for the OLE period | |
| 4.2. Scientific Rationale for Study Design | Added paragraph on rationale for the modified study design | |
| 4.3. Justification for Dose | Added rationale for the OLE dose selection | |
| 5.3. Open-Label Extension Period (newly added section) | Added new criterion 44, 45, and 46 to assess eligibility of participants for the OLE period | |
| 6. Study Intervention | Added table describing authorization as defined by EU-CTR for LY3372689 and placebo, and updated the definition for study intervention | Compliance with EU-CTR |
| | Packaging and Labeling subsection:<br>Added a statement for supply of study interventions by the sponsor or designee in accordance with current Good Manufacturing Practice | |
| | Added treatment regimen table for OLE period | To reflect the changes in the modified open-label study design |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.3. Measures to Minimize Bias: Randomization and Blinding | Added "study periods 2a and 2b" to reiterate the duration of double-blind | Added for clarity |
| | Updated the information in the section based on addition of OLE period | To reflect the changes in the modified open-label study design |
| 6.4. Study Intervention Compliance | Indicated that the telephone visits are applicable only for the double-blind study periods | Added for clarity |
| 6.5.1. Standard of Care for Alzheimer's Disease | Revised visit number for double-blind period from "33" to "29" | Error correction |
| | Specified that approved prescription treatments for AD is permitted but not a requirement in this study | Added for clarity |
| | • New paragraph added for permitted standard-of-care treatments during the OLE period<br>• Added a heading to clearly segregate the double-blind study period and the OLE period (newly added paragraph) | To reflect the changes in the modified open-label study design |
| 6.6. Dose Modification | Updated the information in the section based on OLE | |
| 6.7. Intervention after the End of the Study | | |
| 7.2.1. Discontinuation of Inadvertently Enrolled Participants | Deleted statement which allows inadvertently enrolled participants to receive study intervention | For compliance with sponsor's internal procedure |
| 7.3. Lost to Follow-up | Deleted paragraph on site personnel or an independent third party attempting to collect vital status of participants | |
| | Added a note regarding actions that will be taken by the investigative site personnel when they are unable to contact the participant | Clarification |
| 8.5. Pharmacokinetics | Replaced collection of "serum" with "plasma" samples of LY3372689 | Error correction |
| 8.6.2.1. Exploratory Biomarkers<br>8.8.1. Blood Sample Collection for Exploratory Biomarkers | Added language for additional testing of plasma P-tau217, NFL, and GFAP from the exploratory biomarker samples | Specifying biomarkers to be tested |
| | Added "neuroinflammation" | Clarification |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.6.2.1. Exploratory Biomarkers | Deleted "gene expression of the OGA gene" | Change in assay availability and prioritization of biomarkers for primary data base lock |
| 9. Statistical Considerations<br>9.2. Sample Size Determination | Changed "bMMRM" to "MMRM" | No longer using bMMRM for sensitivity analysis to the primary endpoint nor to other analyses that were previously planned to use bMMRM |
| 9.4.1. General Considerations | Updated the information in the section based on OLE | To reflect the changes in the modified open-label study design |
| | • Added a statement for handling of missing, unused, and spurious data<br>• Deleted duplicate statement | For EU-CTR compliance |
| 9.4.2 Primary Endpoint(s) | Updated to be specific regarding covariates that will be adjusted in the primary analysis and additional sensitivity analysis | For clarify |
| 9.4.3. Secondary Endpoint(s) | Updated the analytic models that will be used for secondary endpoints | To reflect the latest analysis plan for secondary endpoints and for clarity. |
| 9.4.6. Other Safety Analyses(s) | Deleted "Other" from the heading | For clarity |
| 9.5. Interim Analyses | Added statement cross referencing to Section 10.1.6. on timing of dissemination of data summaries | To reinforce awareness of the content in Section 10.1.6. |
| 10.1.1. Regulatory and Ethical Considerations | Added specific statement that the clinical trial will be conducted in compliance with European Regulation (EU) No 536/2014, if applicable | For EU-CTR compliance |
| | Added a bullet point regarding reporting of significant issues related to participant's safety, rights, and data integrity | |
| 10.1.4. Data Protection | Updated the section with required language on data protection | |
| 10.1.6. Dissemination of Clinical Study Data | Added a new paragraph under "Reports" | |
| | Data subsection:<br>• Added " or genetic data" which cannot be provided by the sponsor<br>• Updated the website to submit data request | As per Lilly template requirements |
| 10.1.7. Data Quality Assurance | Updated section | |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 10.2. Appendix 2: Clinical Laboratory Tests | Additional biomarker testing has been included which comprises of NFL, GFAP, and P- tau217 | Specifying biomarkers to be tested |
| 10.3.1. Definition of AE | Updated events meeting the AE definition and events not meeting the AE definition | For EU-CTR compliance |
| 10.3.3. Definition of Product Complaints | Updated definition | As per Lilly template requirements |
| 10.3.6. Regulatory Reporting Requirements | • Updated section<br>• Added a new paragraph to add information for SAE regulatory reporting | For EU-CTR compliance |
| 10.5. Appendix 5: Flortaucipir F18 Tau PET Imaging | • Referenced footnote 'b' for effective dose (mSv) per scan<br>• Deleted footnote 'b' from number of scans in second year | Error correction |
| 10.9. Appendix 9: Abbreviations | Added terms and definitions including abuse, authorized IMP, IMP, medication error, misuse, SoA, and SUSAR | For EU-CTR compliance |
| | Revised "bMMRM" to "MMRM" | No longer using bMMRM for sensitivity analysis to the primary endpoint nor to other analyses that were previously planned to use bMMRM |
| | Added "OLE" to the list | To update list of abbreviations |
| 10.10. Appendix 10: Flortaucipir F18 PET Imaging and MRI Substudy (newly added section) | Added new section for flortaucipir F18 PET imaging and MRI scans substudy which will be performed in approximately 80 participants | To collect additional PET and MRI scans in participants enrolled in the open-label extension period of Study MTAE on a voluntary basis |
| Throughout | Minor formatting and editorial changes | Minor, therefore, not detailed |

**Amendment [b]: (02-Sep-2021)**

This amendment is considered to be nonsubstantial.

**Overall Rationale for the Amendment:**

The main rationale of this amendment is to make an administrative change regarding reference to an unblinded pharmacist.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 6.3 Measures to Minimize Bias: Randomization and Blinding | Removed reference to drug being made available by unblinded site personnel and being given by blinded nurse. Reference to the pharmacy manual also removed. | Minor correction and clarification. |
| | Language corrected regarding blinded and unblinded site personnel for drug dispensing. | |
| | Updated text to use dynamic allocation (minimization) method of Pocock and Simon (1975) in randomization scheme to achieve as much balance as possible across the arms on the stratified factors at the study level. | |
| Section 11 References | Added Pocock and Simon, 1975. | Additional reference for the additions made in Section 6.3. |

**Amendment [a]: (09-Jun-2021)**

**Overall Rationale for the Amendment:**

The main rationale of this amendment is to change the primary endpoint from the CDR-SB to iADRS to improve efficacy signal detection and to add some flexible language for use of P-tau as a screening tool considering the potential limited or delayed availability in some countries. In addition, the mention of specific biomarker assay in exploratory objectives and endpoints has been removed.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.1 Synopsis | Changed primary outcome and language related to P-tau use in screening and as endpoint measure.<br>Removed mention of specific biomarker assay in exploratory objectives and endpoints. | Updated to reflect changes in objectives, Schedule of Activities, and design related to primary endpoint and P-tau. |
| Section 1.3 Schedule of Activities | Clarified study schedule to reflect timing for blood-based exploratory biomarker collections. | To allow for accommodation of emergent technology. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Updated table to add language related to P-tau use in screening and as endpoint measure. | To reflect changes in objectives. |
| | Updated tolerance interval for visit 801. | Correction. |
| Section 3 Objectives and Endpoints | Modified objectives and endpoints to include iADRS assessment as primary objective and CDR-SB assessment as secondary objective. | Primary endpoint changed from CDR-SB to iADRS to reflect recent data reviews suggesting improved capability of iADRS in detecting treatment effects in this population. |
| | Removed mention of specific biomarker assay in exploratory objectives and endpoints. | To allow for accommodation of emergent technology. |
| Section 4.1.1 Lead-In and Screening period (V601 and V1) | Updated wording to clarify that sites can continue with flortaucipir F18 PET scanning without meeting the P-tau screening criterion if the P-tau testing is not available at site. | Added protocol flexibility to allow for not performing P-tau as a prescreen prior to tau PET in cases where it may not be available. All participants will be required to meet P-tau PET criteria for enrollment. |
| Section 4.2 Scientific Rationale for Study Design | Removed text related to CDR-SB. | To remove redundancy and change of endpoint measures. |
| Section 5 Study Population<br>Section 5.1 Inclusion Criteria | Updated wording to allow flexibility for P-tau assay use. Provided information on assay status. | Added protocol flexibility to allow for not performing P-tau as a prescreen prior to tau PET in cases where it may not be available. All participants will be required to meet Tau PET criteria for enrollment. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 6.1 Study Intervention(s) Administered | Corrected visit number. | Error correction. |
| Section 6.3 Measures to Minimize Bias: Randomization and Blinding | Updated text related to stratification of participant randomization. | To allow for potential stratification needs for emerging approved disease-modifying therapies. |
| Section 6.7 Intervention after the End of the Study | Updated text to indicate that an active treatment extension may be offered. | Added flexibility for open-label extension option to be determined at a later date. |
| Section 8.1 Efficacy Assessments | Updated text to include iADRS assessment as primary endpoint analyses and CDR-SB assessment as secondary endpoint analyses.<br>Updated text to indicate that rater should be different for CDR assessment and ADAS-$Cog_{13}$ and MMSE assessments. | To reflect recent data reviews suggesting improved capability of iADRS in detecting treatment effects in this population.<br>Added flexibility. |
| Section 8.6.2 Fluid Measures | Updated text to remove mention of specific assay being used as endpoint measures. | To allow for accommodation of emergent technology. |
| Section 9.2 Sample Size Determination | Updated power calculation to align with the change in primary endpoint. | To reflect change in primary endpoint. |
| Section 9.4 Statistical Analyses | Modified text to include iADRS assessment as primary endpoint analyses and CDR-SB assessment as secondary endpoint analyses. | To reflect recent data reviews suggesting improved capability of iADRS in detecting treatment effects in this population. |
| | Minor edits to the model description for the primary analysis. Added brief description in the statistical model for the sensitivity analysis. | Clarification. |
| Section 10.2 Appendix 2: Clinical Laboratory Tests | Removed plasma NfL, plasma P-tau, and OGA gene expression sample assays. | To allow for accommodation of emergent technology. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 10.8 Appendix 8 Provisions for Changes in Study Conduct During Exceptional Circumstances | Deleted Self-Harm Supplement Form and Self-Harm Follow-Up Form. | Standard Operating Procedures update. |
| Throughout the Protocol | Medical monitor changed to Lilly-designated medical monitor.<br>Minor editorial changes made throughout the protocol. | Correction |

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