Protocol I8D-MC-AZET

A Randomized, Double-Blind, Placebo-Controlled and Delayed-Start Study of LY3314814 in Mild Alzheimer's Disease Dementia (The DAYBREAK Study)

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Confidential Information

LY3314814

AZET is a Phase 3 study designed to test whether LY3314814 will slow disease progression in patients with mild dementia of the Alzheimer's type.

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Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 05-Feb-2016 GMT

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1. Synopsis

Title of Study:

A Randomized, Double-Blind, Placebo-Controlled and Delayed-Start Study of LY3314814 in Mild Alzheimer's Disease Dementia (The DAYBREAK Study)

Rationale:

LY3314814 is a brain-permeable inhibitor of human Beta-site amyloid precursor protein-cleaving enzyme 1 (BACE1/β-secretase). It is being developed for the modification of the clinical course of Alzheimer's disease (AD) by slowing disease progression in patients diagnosed with early Alzheimer's Dementia (which is defined as mild cognitive impairment (MCI) due to AD and mild dementia of the AD type). The current study, I8D-MC-AZET, will enroll patients with mild dementia of the AD type.

Objective(s)/Endpoints:

Placebo-Controlled Period	
Primary Objective	**Endpoints**
To test the hypothesis that LY3314814, administered orally at doses of 20 and 50 mg daily for 78 weeks, will slow the decline of AD as compared with placebo in patients with mild AD dementia	Change in the primary endpoint measure, ADAS-Cog_{13} from baseline to the end of the Placebo- Controlled period
Secondary Objectives	**Endpoints**
Clinical efficacy objectives: • To evaluate the efficacy of LY3314814 on functional, clinical, and cognitive outcomes in patients with mild AD dementia at the end of the Placebo-Controlled period (week 78). The order of testing and control of Type 1 error will be prespecified with a graphical analysis as stated in the Statistical Analysis Plan.	• Functional Outcome Measures o ADCS-iADL score o FAQ • Cognitive/Functional Outcome Measures o iADRS score o CDR-SB • Clinical Outcome Measures o CDR-Global Score o NPI • Cognitive Outcome Measures o MMSE
• To evaluate the relationship between treatment effect of LY3314814 and time (at points other than the end of the Placebo-Controlled period [week 78], such as week 26 and week 52). Specific time points will vary by instrument.	• ADAS-Cog_{13}, ADCS-iADL, FAQ, CDR-SB, and iADRS
• To test the hypothesis that LY3314814 will slow the rate of cognitive and functional decline associated with AD, compared with placebo	• ADAS-Cog_{13}, ADCS-iADL, and FAQ using a slope analysis from a repeated-measures model
• To evaluate the efficacy of LY3314814 to prolong time in the current disease state	• CDR global score
Biomarker objectives: • To evaluate the effect of LY3314814 on CSF Aβ PD markers	• CSF $A\beta_{1-42}$ and $A\beta_{1-40}$ concentrations

• To evaluate the effect of LY3314814 on CSF markers of neurodegeneration	• CSF total tau and phosphorylated tau concentrations
• To evaluate the effect of LY3314814 on brain amyloid burden	• Florbetapir amyloid scan
• To evaluate the effect of LY3314814 on regional cerebral blood flow (rCBF)	• Florbetapir perfusion scan
• To evaluate the effect of LY3314814 on brain aggregated tau levels	• ^{18}F-AV-1451 Tau PET [separate addendum]
• To evaluate the effect of LY3314814 on brain metabolism	• FDG PET regional cerebral metabolic rate of glucose (rCMRg) [separate addendum]
• To evaluate the effect of LY3314814 on brain atrophy	• Brain volumes measured by MRI (vMRI)
Pharmacokinetic objective: • To assess the population PK of LY3314814 and metabolite AZ13569724 in patients with mild AD dementia	• Apparent Oral Clearance of LY3314814 • Central Volume of Distribution of LY3314814
Delayed-Start Period	
Secondary Objectives	**Endpoints**
Primary analysis: To assess if there is a significant difference in mean change from baseline on the primary outcome measure after 6 months of the prespecified Delayed-Start period	The ADAS-Cog$_{13}$ endpoint will be evaluated for the Delayed-Start period following the approach outlined in Liu-Seifert (2015b).
Secondary analyses: • To assess if there is a significant difference in mean change from baseline on the primary outcome measure for the Delayed-Start period at Weeks 117, 130, 143, and 156	• ADAS-Cog$_{13}$ at additional timepoints, following the same approach as for the primary Delayed-Start timepoint.
• The delayed-start analyses as outlined above will be examined at Weeks 104, 117, 130, 143 and, 156 for additional measures of cognition and function	• MMSE, iADRS, ADCS-iADL, and FAQ
Placebo-Controlled and Delayed-Start Periods	
Safety Objective	**Endpoints**
• To evaluate the safety and tolerability of LY3314814 in patients with mild AD dementia	• Standard safety assessments: o spontaneously reported AEs o clinical laboratory tests o vital sign and body weight measurements o 12-lead ECGs o physical examinations including neurological examinations • Additional safety assessments: o Eye examinations o Skin examinations o Serial MRI o C-SSRS

Summary of Study Design:

Study I8D-MC-AZET is a multicenter, randomized, parallel-group, 78-week double-blind, placebo-controlled, study of 2 fixed doses of LY3314814 in patients with mild AD dementia and abnormal levels of amyloid, followed by a 78-week Delayed-Start period.

Treatment Arms and Duration:

There are 4 treatment arms. The randomization ratio is 2:2:1:1 (LY3314814 20 mg: LY3314814 50 mg: Placebo for 78 weeks then LY3314814 20 mg; Placebo for 78 weeks then LY3314814 50 mg). The three treatment groups in the 78-week Placebo-Controlled period include 2 fixed doses of LY3314814 (20 mg or 50 mg) or placebo. In the 78-week Delayed-Start period, there are the same 2 fixed doses of LY3314814 (20 mg or 50 mg) and all patients previously on placebo will then initiate either dose of LY3314814 based on their randomization.

Number of Patients:

Approximately 3800 participants will be screened to achieve 1899 randomized for an estimated total of 633 evaluable participants per treatment group (633 in combined placebo arms during Placebo-Controlled period). If there is an assumed 25% discontinuation rate, approximately 1424 patients will complete the Placebo-Controlled period and 1139 will complete the Delayed-Start period (in which the estimated discontinuation rate is 40% over the entire 3 year study).

Statistical Analysis:

Primary Analyses: The primary objective will be assessed using a mixed-model repeated-measures (MMRM) analysis of the primary endpoint measure, ADAS-Cog_{13}, in which the specific hypothesis is that the decline at the end of the treatment period for at least one dose of LY3314814 will be significantly less than that for placebo. Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.025. All tests of interactions between treatment and other factors will be conducted at an alpha level of 0.05.

The primary analysis of the Delayed-Start period is to assess disease progression between treatment groups from the end of the Placebo-Controlled period to the 6 month time point in the Delayed-Start period. Comparisons of the ADAS-Cog_{13} are made between those patients who were started early on LY3314814 in the Placebo-Controlled period versus those who started LY3314814 in the Delayed-Start period.

Secondary Objectives: A secondary objective of this study and the Placebo-Controlled period is to test the hypothesis that at least one dose of LY3314814 will slow the functional decline (ADCS-iADL and/or FAQ) and/or cognitive/functional outcomes (CDR-SB and/ or iADRS) of AD compared with placebo in patients with mild AD dementia. The MMRM model used in the primary analysis of the Placebo-Controlled period will also be employed for these secondary analyses.

Additional secondary efficacy outcomes beyond function for the Placebo-Controlled period include MMSE and NPI. For each secondary efficacy measure, the change from baseline score at each scheduled post-baseline visit (according to the Study Schedule) during the Placebo-Controlled period will be analyzed using the same MMRM model described for the primary analysis.

An additional MMRM analysis, termed a slopes analysis, will be conducted examining the change from baseline score on the ADAS-Cog_{13}, ADCS-iADL, and FAQ at each scheduled post-baseline visit during the Placebo-Controlled period.

Gatekeeping Strategy: A gatekeeping strategy will be used in Study AZET for testing hypotheses of outcomes to protect against type I error of falsely rejecting a null hypothesis. Gatekeeping will use a prespecified analysis plan that employs Bretz' graphical approach to provide strong control of the study wise Type I error rate for the primary and key secondary hypotheses for the Placebo-Controlled period at level $\alpha = 0.05$ (Bretz et al. 2009; Bretz et al. 2011).

2. Schedule of Activities

Table 2.1. Study Schedule, Protocol I8D-MC-AZET, Visit 1: Preliminary Screening and Screening

Days relative to Study Medication Start	Visit 1 (-60 days to baseline measures)
Preliminary Screening	
Entry and Administrative	
Abbreviated (or full) Informed Consent[a] - participant and study partner	X
Patient number assigned via IxRS	X
Demographics	X
Entry Diagnostics (Study Partner)[b]	
AD8	X
CDR[c]	X
Entry Diagnostics (Patient)[b]	
MMSE	X
CDR[c]	X
Screening	
Entry and Administrative	
Full Informed Consent[a] - participant and study partner	X
Medical /psychiatric History	X
Concomitant treatments	X
Inclusion/exclusion criteria	X
Entry Diagnostics (Patient)	
Amyloid PET (+/- perfusion)[d] *OR*[e] Lumbar puncture[f]	X
Safety Measures	
MRI[d,f]	X
12-Lead ECG[g]	X
Vital signs[h]	X
Height	X
Body weight	X
Adverse events	X
Laboratory Specimens	
Laboratory tests (see Appendix 2)	X
Clinical Exams	
Physical, neurological examinations	X
Comprehensive eye examination[i]	X
Skin examination[j]	X

Study Schedule, Protocol I8D-MC-AZET, Visit 1: Preliminary Screening and Screening

Abbreviations: AD8 = Eight-item Interview to Differentiate Aging and Dementia; CDR = Clinical Dementia Rating; ECG = Electrocardiogram; ICF = Informed Consent Form; IxRS = interactive voice- and web- response system; MMSE = Mini-Mental State Examination; MRI = Magnetic resonance imaging; PET = Positron emission tomography.

[a] A choice to consent in two parts, either a preliminary abbreviated consent followed by the full consent or the full consent given during preliminary screening. After consent is obtained from study partner and patient, all screening procedures may begin and must be completed prior to Visit 2. Due to the extent of the screening procedures they may occur over several days.

[b] The cognitive scales should be the first administered tests in screening. The cognitive tests, at screening, are administered to study partner in the order: 1) AD8 then 2) CDR. The order of testing for the patient is: 1) MMSE then 2) CDR.

[c] The CDR should always be administered to the study partner first and then to the patient; the study partner and patient must be interviewed separately.

[d] Historical amyloid PET scans can be submitted. Note that central reading vendor for this study must confirm amyloid positivity for study eligibility. The MRI and florbetapir F 18 amyloid PET can be performed in any order and can be done on the same day.

[e] If either the florbetapir amyloid scan, historical amyloid PET, or lumbar puncture result is negative for amyloid, patient cannot retest with other diagnostic measure. If either diagnostic is attempted but can't be completed to a final result then the test may be repeated or the alternative test can be used if available.

[f] MRI must be performed before the lumbar puncture for cerebrospinal fluid (CSF) sampling. Both can be performed on same day, central read of MRI results are not required to perform CSF sampling.

[g] Single safety 12-lead ECG recordings will be performed as described in Section 9.4.1.

[h] Vital signs include supine and standing blood pressures and pulse rates, and temperature.

[i] Eye examination must be supervised by an optometrist or ophthalmologist. The baseline examination may be performed any time before randomization. Additional details are described in Section 9.4.7.

[j] Skin examination must be supervised by a dermatologist. The baseline examination may be performed any time before randomization. Additional details are described in Section 9.4.8.

Table 2.2. Study Schedule, Protocol I8D-MC-AZET, Visit 2 through Visit 16 (Placebo-Controlled Period)

Visit No.[a]	V2 Randomization[b]	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	ED[c]
Study week		1	4	7	13	19	26	32[d] ☎	39	45	52	58[d] ☎	65	71	78	
Tolerance interval for Visit (days)		±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Administrative																
Concomitant treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria review	X															
Dispense drug[e]	X	X	X	X	X	X	X		X	X	X		X	X	X	
Assess drug compliance[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Measures (Study Partner)																
FAQ	X						X				X				X	X
ADCS-ADL	X						X				X				X	X
CDR[g]							X				X				X	X
NPI	X						X				X				X	X
EQ-5D	X					X				X					X	X
QoL-AD	X					X				X					X	X
RUD-Lite	X					X				X					X	X
Efficacy Measures (Patient)																
MMSE					X		X				X				X	X
ADAS-Cog_{13}	X				X		X		X		X		X		X	X
RBANS	X									X				X		X
QoL-AD	X					X				X					X	X
CDR[g]							X				X				X	X
Longitudinal Biomarker Measures																
Florbetapir amyloid PET (+/- perfusion) *OR*[h]															X[h]	X[h]
Lumbar puncture[i]														X[i]		X[i]

Visit No.[a]	V2 Randomization[b]	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	ED[c]
Study week		1	4	7	13	19	26	32[d] ☎	39	45	52	58[d] ☎	65	71	78	
Tolerance interval for Visit (days)		±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
MRI															X	X
Safety Measures																
12-Lead ECG[j]	X	X	X		X		X		X		X		X	X	X	X
Vital signs[k]	X	X	X	X	X	X	X		X	X	X		X	X	X	X
Body weight	X				X		X				X				X	X
C-SSRS[l] and Self-Harm Supplement Form	X	X	X	X	X	X	X		X	X	X		X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Specimens																
Blood sample for plasma LY3314814 and AZ13569724 PK[m]			X[m]	X[m]		X[m]			X[m]	X[m]				X[m]		X
Blood sample for plasma biomarkers	X		X				X				X			X		X
ApoE	X															
Laboratory tests (see Appendix 2)	X		X	X	X		X		X		X		X		X	X
Pharmacogenetics	X															
Blood sample for RNA	X						X				X				X	X
Clinical Exams																
Physical, neurological examinations	X		X[n]		X		X[n]		X[n]		X		X[n]		X[n]	X
Comprehensive eye examination[o]											X				X	X
Skin examination[p]					X						X				X	X
Addenda (Optional – site specific)[q]																
FDG PET	X														X	X
OR																
AV-1451 (Tau) PET	X								X						X	X

Study Schedule, Protocol I8D-MC-AZET, Visit 2 through Visit 16 (Placebo-Controlled Period) Abbreviations and Footnotes

Abbreviations: ADAS-Cog_{13} = 13-item Alzheimer's Disease Assessment Scale-Cognition; ADCS-ADL = The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; Aβ = A-beta amyloid; CDR = Clinical Dementia Rating; CSF = Cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = Electrocardiogram; ED = early discontinuation; EQ-5D Proxy = 5-dimensional EuroQol quality of life scale; FAQ = Functional Activities Questionnaire; FDG = fludeoxyglucose; LP = lumbar puncture; MMSE = Mini-Mental State Examination; MRI =Magnetic resonance imaging; NPI = Neuropsychiatric Inventory; PET = Positron emission tomography; PK = Pharmacokinetic; QoL-AD = Quality of Life in Alzheimer's Disease; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RNA = ribonucleic acid; RUD-Lite = Resource Utilization in Dementia-Lite.

[a] Every effort should be made for visits to occur on the designated study days. The overall treatment period in the protocol should be maintained (that is, visits should be scheduled based on the baseline visit rather than the previous visit). Study procedures designated for a specific visit should be performed within 1 day whenever possible. If the time spent at the site needs to be minimized, the assessments can be completed over a longer period.

[b] Patients who meet all study entry criteria will be randomized at Visit 2, but will take the first dose of study treatment the following day (Day 1).

[c] All patients who discontinue study treatment before Visit 30 (Week 156) should have all Early Discontinuation (ED) procedures and assessments performed as soon as possible. ADCS-ADL, FAQ, CDR, MMSE, RBANS, ADAS-Cog_{13}, and NPI tests should be conducted at the early discontinuation visit if it has been more than 12 weeks since these assessments were last administered. Florbetapir amyloid PET, MRI and lumbar puncture, should only be performed if it has been at least 24 weeks since the previous assessment. If both MRI and LP are being done, the MRI must be completed prior to the LP (See FDG-PET or AV-1451 [Tau] PET addendum if applicable). Any patient must also perform the follow-up schedule within 4-6 weeks after last dose of investigational product.

[d] Visits 9 (Week 32) and 13 (Week58) will be conducted by telephone and may include either the patient or the study partner, or both, as appropriate.

[e] First dose to be administered the day after Visit 2 (randomization), preferably in the morning.

[f] The patient 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.

[g] The CDR should always be administered to the study partner first and then to the patient; the study partner and patient must be interviewed separately.

[h] Do either florbetapir amyloid PET or lumbar puncture, whichever was used for entry at screening. If an historical amyloid PET was used to establish amyloid eligibility, a follow up florbetapir amyloid PET should not be performed.

[i] Recommend collecting CSF samples at approximately the same time of day (+/- 4 hours) as prior lumbar punctures. If a post-screen lumbar puncture cannot be obtained because of procedural complications, or patient issues, it will not be considered a protocol violation. In countries prohibiting sample storage, it will not be considered a protocol violation if CSF is not collected for storage and future analysis. Some countries may not collect these samples.

[j] Single safety 12-lead ECG recordings will be performed as described in Section 9.4.1.

[k] Vital signs include supine and standing blood pressures and pulse rates, and temperature.

[l] The Baseline/Screen version of the C-SSRS will be administered at Visit 2 (randomization). All subsequent measures will use the C-SSRS Since Last Visit version. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Lilly Self-Harm Follow-Up (SHFU) form will be used to collect additional information to allow for a more complete assessment of these behaviors.

[m] Please see Section 9.5 for full PK sampling details. May need to call patient in advance for dosing instructions.

[n] *Brief* physical and *full* neurological examinations will be performed at these visits.

[o] Eye examination must be supervised by an optometrist or ophthalmologist. Additional details are described in Section 9.4.7.

[p] Skin examination must be supervised by a dermatologist. Additional details are described in Section 9.4.8.

[q] All patients enrolled in AZET should be considered for either the FDG or AV-1451 (Tau) PET addenda regardless of the method used to establish amyloid positivity at screening.

Table 2.3. Study Schedule, Protocol I8D-MC-AZET, Visit 17 through Visit 30 (Delayed-Start Period)

Visit No.[a]	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28	V29	V30	ED[b]	F/U[c]
Study week	79	82	85	91	97	104	110[d] ☎	117	123	130	136[d] ☎	143	149	156		4-6 wks
Tolerance interval for Visit (days)	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±3
Entry and Administrative																
Concomitant treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense drug[e]		X	X	X	X	X		X	X	X		X	X			
Assess drug compliance[f]	X	X	X	X	X	X	X[f]	X	X	X	X[f]	X	X	X	X	
Efficacy Measures (Study Partner)																
FAQ						X				X				X	X	
ADCS-ADL						X				X				X	X	
CDR[g]						X				X				X	X	
NPI						X				X				X	X	
EQ-5D					X				X					X	X	
QoL-AD					X				X					X	X	
RUD-Lite					X				X					X	X	
Efficacy Measures (Patient)																
MMSE				X		X				X				X	X	
ADAS-Cog_{13}				X		X		X		X		X		X	X	
RBANS									X				X		X	
QoL-AD					X				X					X	X	
CDR[f]						X				X				X	X	
Additional Efficacy Measures																
Florbetapir amyloid PET (+/-perfusion) *OR*[h]														X[h]	X[h]	
Lumbar puncture[i]													X[i]		X[i]	
MRI														X	X	

Safety Measures																
12-Lead ECG[j]	X	X		X		X		X		X		X	X	X	X	X
Vital signs[k]	X	X	X	X	X	X		X	X	X		X	X	X	X	X
Body weight				X		X				X				X	X	
C-SSRS[l] and Self-Harm Supplement Form	X	X	X	X	X	X		X	X	X		X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Specimens																
Blood sample for plasma biomarkers						X				X			X		X	
Blood sample for RNA						X				X				X	X	
Laboratory tests (see Appendix 2)		X	X	X		X		X		X		X		X	X	
Clinical Exams																
Physical, neurological examinations		X[m]		X		X[m]		X[m]		X		X[m]		X[m]	X	
Comprehensive eye examination[n]										X				X	X	
Skin examination[o]				X						X				X	X	
Addenda																
FDG PET OR[p] AV-1451 (Tau) PET														X	X	

Study Schedule, Protocol I8D-MC-AZET, Visit 17 through Visit 30 (Delayed-Start Period) Abbreviations and Footnotes

Abbreviations: ADAS-Cog = 13-item Alzheimer's Disease Assessment Scale-Cognition; ADCS-ADL = The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; Aβ = A-beta amyloid; CDR = Clinical Dementia Rating; CSF = Cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = Electrocardiogram; ED = early discontinuation; EQ-5D Proxy = 5-dimensional EuroQol quality of life scale; FAQ = Functional Activities Questionnaire; FDG = fludeoxyglucose; F/U = Follow-up; LP = lumbar puncture; MMSE = Mini-Mental State Examination; MRI = Magnetic resonance imaging; NPI = Neuropsychiatric Inventory; PET = Positron emission tomography; PK = Pharmacokinetic; QoL-AD = Quality of Life in Alzheimer's Disease; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RNA = ribonucleic acid; RUD-Lite = Resource Utilization in Dementia-Lite.

[a] Every effort should be made for visits to occur on the designated study days. The overall treatment period in the protocol should be maintained (that is, visits should be scheduled based on the baseline visit rather than the previous visit). Study procedures designated for a specific visit should be performed within 1 day whenever possible. If the time spent at the site needs to be minimized, the assessments can be completed over a longer period.

[b] All patients who discontinue study treatment before Visit 30 (Week 156) should have Early Discontinuation (ED) procedures and assessments performed as soon as possible. ADCS-ADL, FAQ, CDR, MMSE, RBANS, ADAS-Cog_{13}, and NPI tests should be conducted at the early discontinuation visit if it has been more than 12 weeks since they were last administered. Florbetapir amyloid PET, MRI and lumbar puncture, should only be performed if it has been at least 24 weeks since the previous assessment. If both MRI and LP are being done, the MRI should be completed prior to the LP (See FDG-PET or AV-1451 [Tau] PET addendum if applicable).

[c] Follow-up should be scheduled to occur 4-6 weeks after the last dose of investigational product.

[d] Visit 23 and 27 (Week 110 and 136) will be conducted by telephone and may include either the patient or the study partner, or both, as appropriate and the patient or study partner may be required to visit the clinic within ±1 week of the visit for drug dispensing.

[e] First dose to be administered the day after Visit 2 (randomization), preferably in the morning.

[f] The patient should be instructed to retain all empty drug kits after using up the medication in the kit and to bring the empty kits and any unused medication to the clinic at each visit.

[g] The CDR should always be administered to the study partner first and then to the patient; the study partner and patient must be interviewed separately. The assessments should be performed at the same time of day, if possible.

[h] Do either florbetapir amyloid PET or Lumbar puncture, whichever was used for entry at screening. If an historical amyloid PET was used to establish amyloid for patient eligibility, a follow up florbetapir amyloid PET should not be performed.

[i] Recommend collecting CSF samples at approximately the same time of day (+/- 4 hours) as prior lumbar punctures. If a post-screen lumbar puncture cannot be obtained because of procedural complications, patient issues, or patient request, it will not be considered a protocol violation. In countries prohibiting sample storage, it will not be considered a protocol violation if CSF is not collected for storage and future analysis. Some countries may not collect these samples.

[j] Single safety 12-lead ECG recordings will be performed as described in Section 9.4.1.

[k] Vital signs include supine and standing blood pressures and pulse rates, and temperature.

[l] The C-SSRS Since Last Visit version will be administered at every visit. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Lilly Self-Harm Follow-Up (SHFU) form will be used to collect additional information to allow for a more complete assessment of these behaviors.

[m] Brief physical and full neurological examinations will be performed at these visits.
[n] Eye examination must be supervised by an optometrist or ophthalmologist. Additional details are described in Section 9.4.7.
[o] Skin examination must be supervised by a dermatologist. Additional details are described in Section 9.4.8.
[p] All patients enrolled in AZET should be considered for either the FDG or AV-1451 (Tau) addenda regardless of the method used to establish amyloid positivity.

3. Introduction

3.1. Study Rationale

LY3314814 (AZD3293) is a brain-permeable inhibitor of human Beta-site amyloid precursor protein-cleaving enzyme 1 (BACE1/β-secretase). It is being developed for the modification of the clinical course of Alzheimer's disease (AD) by slowing disease progression in patients diagnosed with early Alzheimer's Dementia (which is defined as mild cognitive impairment (MCI) due to AD and mild dementia of the AD type). The current study, I8D-MC-AZET, will enroll patients with mild dementia of the AD type.

3.2. Background

Alzheimer's disease is a progressive and fatal neurodegenerative disease manifested by cognitive deterioration in addition to progressive impairment of activities of daily living. Current treatments are seen as minimally effective, with only minor symptomatic improvements for a limited duration, and they do not slow the progression of the disease.

Alzheimer's disease pathology is characterized by the formation of amyloid plaques and neurofibrillary tangles. These pathologies are associated with an inflammatory response, together with loss of neurons and synapses in the neocortex, hippocampus, and other subcortical regions of the brain. Cleavage of amyloid precursor protein (APP) by proteases known as secretases (β and γ) gives rise to the group of peptide fragments known as Aβ. They are the main components of the amyloid plaques. Further, mutations or duplications of the APP gene constitute a genetic link to Familial AD. BACE1 is a type I transmembrane aspartic acid protease related to the pepsin and retroviral aspartic protease families. BACE1 cleaves APP at the β-secretase site, and APP is then cleaved by γ-secretase generating Aβ peptides.

Based on its key role in the amyloid cascade, BACE1 is considered to be a promising therapeutic target for slowing disease progression in AD. BACE1 inhibitors would be expected to prevent the generation of Aβ peptides and, consequently, reduce the detrimental effects of Aβ toxicity and the progressive formation of amyloid plaques in the brain.

As a potent inhibitor of BACE1, LY3314814 is a potential disease-modifying therapy for the treatment of AD. LY3314814 has been shown to reduce $A\beta_{1-40}$ and $A\beta_{1-42}$ in mice, rats, guinea pigs, dogs, and humans. At sufficient exposures, LY3314814 reduces Aβ levels in the brain and cerebrospinal fluid (CSF).

Study AZET is the second Phase 3 study in the LY3314814 registration program. It will be conducted in patients with mild AD dementia.

3.3. Benefit/Risk Assessment

To date, no safety issues have been identified that would create an unfavorable benefit-risk balance for LY3314814. The potential benefits are not established but expectation for an effect in slowing AD progression is described above in the Section 3.2. Potential risks include but are not limited to elevated liver enzymes, QT-prolongation with overdose, skin or hair hypopigmentation, rash, retinal changes, and potential interactions with other drugs. The potential risks are monitored with scheduled labs, electrocardiograms (ECGs), skin exams, eye exams, and restrictions on some concomitant medications. More information about the known

and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY3314814 can be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

Table 4.1 shows the objectives and endpoints of the study.

Table 4.1. Objectives and Endpoints

Placebo-Controlled Period	
Primary Objective	**Endpoints**
To test the hypothesis that LY3314814, administered orally at doses of 20 and 50 mg daily for 78 weeks, will slow the decline of AD as compared with placebo in patients with mild AD dementia	Change in the primary endpoint measure, ADAS-Cog_{13} from baseline to the end of the Placebo- Controlled period
Secondary Objectives	**Endpoints**

Clinical efficacy objectives:
• To evaluate the efficacy of LY3314814 on functional, clinical, and cognitive outcomes in patients with mild AD dementia at the end of the Placebo-Controlled period (week 78). The order of testing and control of Type 1 error will be prespecified with a graphical analysis as stated in the Statistical Analysis Plan.
	• Functional Outcome Measures
	  ○ ADCS-iADL score
	  ○ FAQ
	• Cognitive/Functional Outcome Measures
	  ○ iADRS score
	  ○ CDR-SB
	• Clinical Outcome Measures
	  ○ CDR-Global Score
	  ○ NPI
	• Cognitive Outcome Measures
	  ○ MMSE

• To evaluate the relationship between treatment effect of LY3314814 and time (at points other than the end of the Placebo-Controlled period [week 78], such as week 26 and week 52). Specific time points will vary by instrument.	• ADAS-Cog_{13}, ADCS-iADL, FAQ, CDR-SB, and iADRS
• To test the hypothesis that LY3314814 will slow the rate of cognitive and functional decline associated with AD, compared with placebo	• ADAS-Cog_{13}, ADCS-iADL, and FAQ using a slope analysis from a repeated-measures model
• To evaluate the efficacy of LY3314814 to prolong time in the current disease state	• CDR global score
Biomarker objectives: • To evaluate the effect of LY3314814 on CSF Aβ PD markers	• CSF $A\beta_{1-42}$ and $A\beta_{1-40}$ concentrations
• To evaluate the effect of LY3314814 on CSF markers of neurodegeneration	• CSF total tau and phosphorylated tau concentrations
• To evaluate the effect of LY3314814 on brain amyloid burden	• Florbetapir amyloid scan
• To evaluate the effect of LY3314814 on regional cerebral blood flow (rCBF)	• Florbetapir perfusion scan
• To evaluate the effect of LY3314814 on brain aggregated tau levels	• ^{18}F-AV-1451 Tau PET [separate addendum]
• To evaluate the effect of LY3314814 on brain metabolism	• FDG PET regional cerebral metabolic rate of glucose (rCMRg) [separate addendum]

• To evaluate the effect of LY3314814 on brain atrophy	• Brain volumes measured by MRI (vMRI)
Pharmacokinetic objective: • To assess the population PK of LY3314814 and metabolite AZ13569724 in patients with mild AD dementia	• Apparent Oral Clearance of LY3314814 • Central Volume of Distribution of LY3314814
Delayed-Start Period	
Secondary Objectives	**Endpoints**
Primary analysis: To assess if there is a significant difference in mean change from baseline on the primary outcome measure after 6 months of the prespecified Delayed-Start period	The ADAS-Cog_{13} endpoint will be evaluated for the Delayed-Start period following the approach outlined in Liu-Seifert (2015b).
Secondary analyses: • To assess if there is a significant difference in mean change from baseline on the primary outcome measure for the Delayed-Start period at Weeks 117, 130, 143, and 156	• ADAS-Cog_{13} at additional timepoints, following the same approach as for the primary Delayed-Start timepoint.
• The delayed-start analyses as outlined above will be examined at Weeks 104, 117, 130, 143 and, 156 for additional measures of cognition and function	• MMSE, iADRS, ADCS-iADL, and FAQ
Placebo-Controlled and Delayed-Start Periods	
Safety Objective	**Endpoints**
• To evaluate the safety and tolerability of LY3314814 in patients with mild AD dementia	• Standard safety assessments: o spontaneously reported AEs o clinical laboratory tests o vital sign and body weight measurements o 12-lead ECGs o physical examinations including neurological examinations • Additional safety assessments: o Eye examinations o Skin examinations o Serial MRI o C-SSRS

Abbreviations: AD = Alzheimer's disease; ADAS-Cog_{13} = 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-iADL = Alzheimer´s Disease Cooperative Study Activities of Daily Living Inventory instrumental items score; CDR-SB = Clinical Dementia Rating Sum of Boxes; CI = confidence interval; CSF = cerebrospinal fluid; DNA = deoxyribonucleic acid; FAQ = Functional Activities Questionnaire; FDG = Fludeoxyglucose; iADRS = integrated Alzheimer's Disease Rating Scale; MMRM = mixed-model repeated-measures; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; PET = positron emission tomography; PK = pharmacokinetic; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RUD-Lite = Resource Utilization in Dementia – Lite.

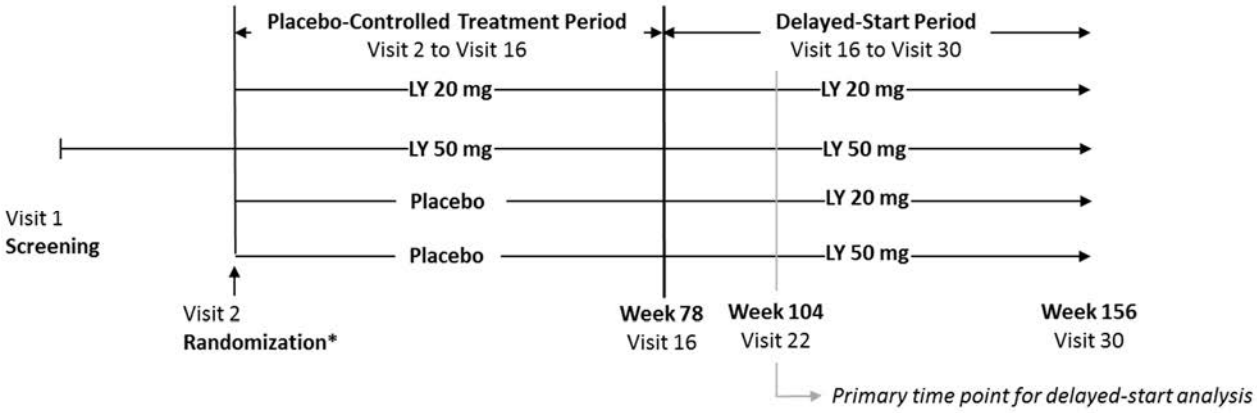
5. Study Design

5.1. Overall Design

Study I8D-MC-AZET (AZET) is a multicenter, randomized, parallel-group, 78-week double-blind, placebo-controlled, comparison of 2 fixed doses of LY3314814 (20 mg or 50 mg) in patients with mild AD dementia and abnormal levels of amyloid, followed by a 78-week Delayed-Start period. There are 4 treatment arms. The randomization ratio is 2:2:1:1 (LY3314814 20 mg: LY3314814 50 mg: Placebo for 78 weeks then LY3314814 20 mg; Placebo for 78 weeks then LY3314814 50 mg). The screening for this study can be done in 2 parts, if the investigator chooses, and additional details can be found in Section 2.

The purpose of the Delayed-Start period is to assess whether LY3314814 has an effect independent of acute symptomatic effects otherwise consistent with disease-modification or slowing of disease progression. The objective is to determine whether patients starting LY3314814 78 weeks later can achieve the same outcome as those starting LY3314814 at the beginning of Visit 2. The objective will be evaluated using all available data through Week 104 (that is, 6 months into the Delayed-Start period) by the time of database lock of the Placebo-Controlled treatment period.

Figure 5.1 illustrates the study design.



Abbreviations: LY=LY3314814

*At Visit 2, patients randomized to placebo in the Placebo-Controlled treatment period will also be randomly assigned to a Delayed-Start treatment group to begin at Week 78. This will be achieved by randomizing patients to one of four sequences in a randomization ratio of 2:2:1:1 (LY3314814 20 mg: LY3314814 50 mg: Placebo then LY3314814 20 mg; Placebo then LY3314814 50 mg). The primary analysis of the Placebo-Controlled treatment period will occur at Visit 16 (Week 78). The primary analysis of the Delayed-Start period will occur at Visit 22 (Week 104).

Figure 5.1. Illustration of study design for Clinical Protocol I8D-MC-AZET.

5.2. Number of Participants

Approximately 3800 participants will be screened to achieve 1899 randomized for an estimated total of 633 evaluable participants per treatment group (633 in combined placebo arms during

Placebo-Controlled period). If there is an assumed 25% discontinuation rate, approximately 1424 patients will complete the Placebo-Controlled period and 1139 will complete the Delayed-Start period (in which the estimated discontinuation rate is 40% over the entire 3 year study).

5.3. End of Study Definition

End of the trial for the Placebo-Controlled period primary outcome measure is the date of the last visit or last scheduled procedure for Visit 16 (Week 78) shown in the Schedule of Activities (Section 2) for the last patient. End of the trial for the Delayed-Start period primary outcome measure occurs simultaneously with the end of the trial for the Placebo-Controlled period but includes all available data through Visit 22 (Week 104). End of AZET study for the Delayed-Start period secondary outcomes is the date of the last visit or last scheduled procedure for Visit 30 (Week 156) shown in the Schedule of Activities (Section 2) for the last patient.

5.4. Scientific Rationale for Study Design

Study AZET is designed as a second Phase 3 study to be initiated after a safety interim analysis of an ongoing Phase 2/3 study [I8D-MC-AZES] in an early AD population. Study AZET will only enroll mild AD dementia patients. The study is 18 months in duration for the primary outcome of the Placebo-Controlled period. Studies of this duration, in mild AD dementia patients, are of sufficient time to detect a difference from the placebo decline rate (Liu-Seifert et al. 2015a). Following the Placebo-Controlled period, the placebo patients will take either the 20-mg or 50-mg dose of LY3314814. Allocation to placebo or drug, and dose allocation blinds are maintained for patient and site. During this Delayed-Start period, data from randomization (Visit 2) through the initial 6 months of therapy (Week 104) will be used to test whether there is a prespecified treatment effect that cannot be achieved with the later start of treatment. The time points beyond the primary analysis at 6 months of the Delayed-Start period will be analyzed upon last patient visit for Visit 30 to determine the robustness of early treatment over the full 18-month delayed-period.

5.5. Justification for Dose

LY3314814 is administered orally at doses of 20 and 50 mg daily and the doses were selected based on preclinical and pharmacodynamic (PD) data. The projected therapeutic dose range is based on levels of inhibition of BACE1 in the central nervous system as calculated from the multiple-ascending-dose study of CSF Aβ data. It is anticipated that 20-mg and 50-mg LY3314814 doses should achieve clinically relevant CSF Aβ reductions, and the projected mean exposures at those doses should be well within the range of exposures shown to be safe and well tolerated in the Phase 1 studies and ongoing Phase 2/3 study [I8D-MC-AZES]. From Phase 1 data, the 20-mg dose is predicted to provide >50% mean reduction in CSF $A\beta_{1-42}$ concentrations over the dosing interval, and the 50-mg dose is predicted to provide approximately 75% reduction in CSF $A\beta_{1-42}$ concentrations over the dosing interval. Thus, these 2 doses are deemed sufficient to lower CSF $A\beta_{1-42}$ concentrations to a level that will lead to a demonstration of efficacy of LY3314814 in this study based on human genetic data (Jonsson et al. 2012). The pharmacokinetic (PK) variability is expected to be sufficiently low to ensure that individual

patient exposures at these doses will also not exceed the levels already demonstrated to be safe and well tolerated.

6. Study Population

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

6.1. Inclusion Criteria

Patients with mild AD dementia are eligible to be included in the study only if they meet all of the following criteria at screening.

General Criteria

[1] Provision of signed and dated informed consent form (ICF) from patient (or legal representative if required) and from study partner prior to any study-specific procedures being performed

[2] Male or female, aged 55 to 85 years inclusive at the time of signing ICF

Diagnostic Criteria

[3] Patient must meet the National Institute on Aging (NIA) and the Alzheimer's Association (AA) (NIA-AA) criteria for probable AD dementia (McKhann et al. 2011)

[4] Mini-Mental State Examination (MMSE) score of 20 to 26 inclusive at screening visit

[5] For a diagnosis of mild AD dementia, patient must have a Clinical Dementia Rating (CDR) global score of 0.5 or 1, with the memory box score ≥0.5 at screening

[6] Florbetapir F 18 positron emission tomography (PET) or CSF $A\beta_{1-42}$ positive by central assessor for presence of amyloid

Note: Historical amyloid PET scans can be submitted. Note that central reading vendor for this study must confirm amyloid positivity for study eligibility. If either the florbetapir PET, historical amyloid PET or CSF $A\beta_{1-42}$ result is negative for amyloid, patient cannot retest with other diagnostic measure. If either diagnostic is attempted but can't be completed to a final result then the test may be repeated or the alternative test can be used if available.

Contraception

[7] Women must be postmenopausal, surgically sterile, or having infertility due to congenital anomaly. A postmenopausal woman is defined as either having an intact uterus with at least 6 months of spontaneous amenorrhea or a diagnosis of menopause prior to starting hormone replacement therapy. Surgically sterile women are defined as those who have had a hysterectomy, bilateral ovariectomy (oophorectomy), or bilateral tubal ligation.

[8] Men with pregnant partners should use condoms from the first day of dosing until 3 months after the last dose of study treatment and abstain for 24 hours after dose administration of the florbetapir, AV-1451 or fludeoxyglucose (FDG) PET tracer.

Men with partners of childbearing potential must abstain or use condoms plus an additional effective form of contraception from the first day of dosing until 3 months after the last dose of study treatment and abstain for 24 hours after dose administration of the florbetapir, AV-1451 or FDG PET tracer. For this protocol, sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. True abstinence is only acceptable when it is in line with the patient's usual and preferred lifestyle.

Note: The subject may choose to use a double–barrier method of contraception. (Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide [that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide]. It should be noted, however, that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined).

Concomitant Medication Criteria

[9] All medication dosing should be stable for at least 30 days before screening, and between screening and randomization (does not apply to medications discontinued)

Procedural Criteria

[10] Must have completed 6 years of formal education and/or have a history of academic achievement and/or employment sufficient to exclude lifelong intellectual disability

[11] The patient must have a reliable study partner with whom he/she cohabits or has regular contact (combination of face-to-face visits/ telephone contact acceptable). If at all possible, the same study partner should be willing to participate in study visits to provide meaningful input into the rating scales administered in this study, where study partner input is required or be available by telephone and must have sufficient patient interaction. As guidance, the ability for a study partner to meet his/her expected responsibilities for this study would normally be possible when the study partner spends no less than 10 hours per week with the subject, divided over multiple days.

[12] Patient and study partner must be able to read, write, and speak the language in which psychometric tests are provided, with acceptable visual and auditory acuity (corrected)

[13] Study partner must be cognitively able to fulfill the requirements of the study, in the opinion of the investigator

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

Medical Conditions

[14] Significant and/or current neurological disease affecting the central nervous system, other than AD, that may affect cognition or ability to complete the study, including but not limited to, other dementias, repetitive head trauma, serious infection of the brain, Parkinson's disease, epilepsy, or cervicocranial vascular disease.

[15] Patients 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 patient's ability to complete the study. Patients with history of schizophrenia or other chronic psychosis are excluded.

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

[17] Within 1 year before the screening visit or between screening and randomization, any of the following: myocardial infarction; moderate or severe congestive heart failure, New York Heart Association class III or IV; hospitalization for, or symptoms of, unstable angina; syncope due to orthostatic hypotension or unexplained syncope; known significant structural heart disease (such as, significant valvular disease, hypertrophic cardiomyopathy); or hospitalization for arrhythmia

[18] Congenital QT prolongation

[19] Intermittent second- or third-degree atrioventricular (AV) heart block or AV dissociation or history of ventricular tachycardia

[20] A corrected QT (QTcF) interval measurement >470 msec (men and women) at screening (as determined at the investigational site)

[21] History of malignant cancer within the last 5 years

Note: The following is a partial list of conditions that are permissible for study entry: non-metastatic basal and/or squamous cell carcinoma of the skin, in situ cervical, or non-progressive prostate cancer

[22] Current serious or unstable clinically important systemic illness that, in the judgment of the investigator, is likely to affect cognitive assessment, deteriorate, or affect the patient's safety or ability to complete the study, including hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, immunologic, or hematologic disorders

[23] History of vitiligo and/or current evidence of post-inflammatory hypopigmentation

[24] Severe drug allergy or anaphylaxis to 2 or more drugs classes

[25] Screening magnetic resonance imaging (MRI) shows evidence of >5 microhemorrhages; prior macrohemorrhage (>1 cm^3); ≥4 infarcts, evidence of cerebral contusion, encephalomalacia, space-occupying lesion with mass-effect and edema

Note: Cortical superficial siderosis is not an exclusion.

[26] Uncontrolled hypertension, that is, supine systolic blood pressure >165 mmHg or diastolic blood pressure >95 mmHg. If an initial blood pressure reading is higher than this, an additional attempt (at this visit or on another day) could be used before excluding a patient for uncontrolled hypertension.

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

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

Patients with past history (suspected or confirmed) of Hepatitis C (resolved >6 months prior to enrollment) should have hepatitis C virus (HCV) ribonucleic acid (RNA) polymerase chain reaction (PCR) testing at screening and are excluded if HCV RNA PCR is positive.

Patients in high-prevalence regions may be required to have screening serology.

[29] Any clinically important abnormality at screening, as determined by investigator, in physical or neurological examination, vital sign, ECG, or clinical laboratory test results that could be detrimental to the patient or could compromise the study

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

[31] Alanine aminotransferase (ALT) ≥2x the upper limit of normal (ULN) of the performing laboratory, aspartate aminotransferase (AST) ≥2x ULN, total bilirubin ≥1.5x ULN, or alkaline phosphatase (ALP) ≥1.5x ULN at screening

NOTE: Patients with total bilirubin ≥1.5 x ULN are not excluded if they meet all of the following criteria for Gilbert syndrome:

1. Bilirubin is predominantly indirect (unconjugated) at screening (direct bilirubin within normal limits)
2. Absence of liver disease
3. ALT, AST, and ALP ≤1x ULN at screening
4. Hemoglobin not significantly decreased at screening

Prior/Concomitant Therapy (see Operations Manual for excluded medications)

[32] Use of strong inhibitors of CYP3A4 or of strong inducers of CYP3A4 within 30 days before randomization

[33] Use of strong inhibitors of P-glycoprotein (Pgp) or breast cancer resistance protein (BCRP) or inducers of Pgp or sensitive Pgp substrates that may prolong the QT interval within 30 days before randomization

Procedural

[34] Has any contraindications for MRI studies

Additional exclusion criteria for patients undergoing CSF sampling:

[35] Has any contraindication for lumbar puncture including clinically significant abnormal findings in laboratory assessments of coagulation or hematology or use of medications known to significantly influence coagulation, such as warfarin or heparin

Additional exclusion criteria for patients using PET for inclusion are as follows:

[36] Planning to have exposure to ionizing radiation that, in combination with the planned administration of study PET ligand(s), would result in a cumulative exposure that exceeds local recommended exposure limits

[37] Hypersensitivity to florbetapir F 18

Prior/Concurrent Clinical Trial Experience

[38] Currently enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study

[39] Previously completed or withdrawn from this study or any other study investigating LY3314814

[40] Treatment with any investigational drug or device within 30 days or 5 half-lives prior to screening (whichever is longer)

[41] Prior treatment with an AD vaccine. Prior treatment with a passive anti-amyloid immunotherapy is allowed if completed at least 5 half-lives prior to randomization.

Other Exclusions

[42] 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.

[43] Lilly or AstraZeneca employees or employees of any third-party organizations (TPOs) involved in study who require exclusion of their employees, or have caregivers who are Lilly employees or are employees of any TPOs involved in study who required exclusions of their employees

6.3. Lifestyle Restrictions

1. Refrain from donating blood or sperm from the screening visit until 3 months after the follow-up visit
2. Follow restrictions regarding concomitant medications according to Section 7.7 and AZET operations manual
3. Avoid use of tanning beds and self-tanning products
4. Wear a hat and appropriate clothing when exposed to sunlight; use a sunscreen with a skin protection factor (SPF) of at least 15; and protect the lips with a lip balm containing sun block

5. Men with pregnant partners should use condoms from the first day of dosing until 3 months after the last dose of study treatment and abstain for 24 hours after dose administration of the florbetapir, AV-1451 or FDG PET tracer.
   Men with partners of childbearing potential must abstain or use condoms plus an additional effective form of contraception from the first day of dosing until 3 months after the last dose of study treatment and abstain for 24 hours after dose administration of the florbetapir, AV-1451 or FDG PET tracer. For this protocol, sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. True abstinence is only acceptable when it is in line with the patient's usual and preferred lifestyle.
6. Avoid excessive use of alcohol from the screening visit until study end. 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.

6.4. Screen Failures

Patients who do not meet the criteria for participation in this study (screen failure) for the following reasons may be rescreened two times:

- Patients who required treatment for an acute illness that resolved (for example, a urinary tract infection) or had stabilization of a chronic medical problem (for example, uncontrolled hypertension)
- Patients who are not on a stable dose of a concomitant medication prior to randomization may be re-screened once the stable dose criteria have been met
- Patients who require more time to identify an appropriate study partner
- Patients who are unable to complete screening procedures in a timely manner
- Patients who screen-fail for MMSE >26, may be rescreened after 6 months, if the investigator feels there has been further cognitive decline.

When re-screening is performed in the above circumstances, new informed consent form(s) (ICF) must be signed and will be assigned a new identification number and all inclusion and exclusion criteria must be met.

6.5. Study Partner

Every patient in the study must have a study partner. An identification code will be assigned to each study partner and recorded for each efficacy measure that the study partner provides input. Demographic data, including relationship to the patient, will be collected for every study partner. Several of the efficacy measures require input from the study partner. The study partner should be willing to participate in every study visit that requires their input for efficacy measures as outlined in Section 2. The study partner is not required to attend all study procedures; examples include but are not limited to MRI, PET or lumbar procedures, skin or eye examinations. While

every effort should be made to maintain the same study partner for a given patient throughout the study, in the event of an unavoidable change in study partner, the new study partner should be thoroughly oriented to the purpose and requirements of the study, sign consent and be assigned a new identification code.

7. Treatments

7.1. Treatments Administered

LY3314814 film-coated tablets in two different strengths (20 and 50 mg) and matching placebo will be manufactured and provided by AstraZeneca.

Investigational product will be dispensed as outlined in the Schedule of Activities (Section 2). Since the LY3314814 20 mg tablets and the LY3314814 50 mg tablets look different, the investigational product will be blinded using double-dummy technique. For study treatments (blinded) during the Placebo-Controlled treatment period see (Visit 2 to Visit 16) Table 7.1.

For study treatments (blinded) during the Delayed-Start Period (Visit 16 to 30), patients who were on placebo will be switched to either LY3314814 20 mg or LY3314814 50 mg; blinding is maintained to prior allocation and dose (see Table 7.1).

Table 7.1. Treatment Regimens for Placebo-Controlled and Delayed-Start Periods

Regimen	Placebo-Controlled Period Dose (Visit 2 through Visit 16)	Delayed-Start Period Dose (Visit 16 through Visit 30)
LY Dose Group 1	20 mg LY Placebo to Match 50mg LY	20 mg LY Placebo to Match 50mg LY
LY Dose Group 2	50 mg LY Placebo to Match 20mg LY	50 mg LY Placebo to Match 20mg LY
Placebo	Placebo to Match 20mg LY Placebo to Match 50mg LY	20 mg LY and Placebo to Match 50mg LY OR 50 mg LY and Placebo to Match 20mg LY

Abbreviations: LY=LY3314814

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational product to the patient
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- at the end of the study returning all unused medication to the Sponsor, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labelling

All study medication will be provided in child resistant blister packs. The blisters will be further packed into patient compliance kits. Each kit will have a unique kit number. Enough tablets will be dispensed for daily dosing until the patient returns for the next study visit.

All randomized study material will be labeled with either a booklet label or a single panel (country specific) label. All labels will be translated into local language and prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labelling.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web- and voice-response system (IxRS). The IxRS will be used to assign the package containing double-blind investigational product to each patient. Site personnel will confirm that they have located the correct package by entering a confirmation number found on the packages into the IxRS. Specific information concerning the use of the IxRS will be provided to the investigators.

To achieve between-group comparability for site factor, the randomization will be stratified by site.

7.2.1. Selection and Timing of Doses

Patient is to take the first dose the day after randomization. The dose is to be taken once daily, preferably in the morning unless instructed otherwise (See Section 9.5 and Section 2 for changes in typical timing).

7.3. Blinding

This is a double-blind study, with a Placebo-Controlled period and a period without placebo (Delayed-Start period). Both patients and site personnel will remain blind to dose and prior allocation of placebo throughout the study.

To preserve the blinding of the study, a minimum number of the Sponsor personnel will see the randomization table and treatment assignments before the study is complete.

Emergency unblinding for AEs may be performed through the IxRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IxRS.

If an investigator, site personnel performing assessments, or patient is unblinded in the Placebo-Controlled period, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Sponsor-designated medical monitor for the patient to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor clinical research physician (CRP) prior to unblinding a patient's treatment assignment unless this could delay

emergency treatment of the patient. If a patient's treatment assignment is unblinded, the Sponsor must be notified immediately.

7.4. Dosage Modification

Dose adjustments are not permitted in this study.

7.5. Preparation/Handling/Storage/Accountability

All study medication must be kept in a secure place under appropriate storage conditions.

Appropriate storage conditions are specified on the study medication label.

The study medication provided for this study will only be used as directed in the study protocol. The study site personnel will account for all study medications dispensed to and returned from the patient.

Study site personnel will account for all study medications received at the site, unused study medications and for appropriate destruction. Certificates of delivery, destruction and return should be signed.

7.6. Treatment Compliance

Patient compliance with study medication will be assessed at each visit by direct questioning and counting returned tablets. The patient 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 will be assessed at telephone visits via questioning of the patient and/or study partner.

Patients who consume at least 80% of the prescribed daily dose during this study will be considered compliant. Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication. Patients regarded as non-compliant may be discontinued at the investigator's discretion, in consultation with the medical monitor.

7.7. Concomitant Therapy

The list of excluded medications is provided in a separate Operations Manual.

Concomitant medications with the potential to affect cognition are permitted, provided the patient has been maintained on a stable dose regimen for at least 30 days before screening, and between screening and randomization. After randomization, attempts should be made to maintain stable doses of symptomatic Alzheimer's disease medication, however, changes or additions are permitted when clinically indicated and must be documented in eCRF.

The following are prohibited concomitant medications during the study:

- Use of any investigational drug or device not specified in this study

- Use of any drug of abuse, including but not limited to cannabis, illicit amphetamine, cocaine, illicit opiates, propoxyphene, methadone, methaqualone, phencyclidine, or illicit barbiturate
- Use of any anticonvulsant or antiparkinson medication, unless used for nonexcluded medical conditions such as pain or restless leg syndrome
- Use of depigmenting agents, such as, hydroquinone
- Use of strong inhibitors or inducers of CYP3A4 (topical may be permitted)
- Use of strong inhibitors of Pgp or BCRP or inducers of Pgp (topical may be permitted)
- Use of drugs known to be sensitive Pgp substrates that may prolong the QT interval (topical may be permitted).

7.8. Treatment after the End of the Study

7.8.1. Study Extensions

There is not currently a plan to extend the study beyond Visit 30.

7.8.2. Continued Access

LY3314814 may be made available to patients who have completed the Delayed-Start period and are still receiving benefit from study treatment until LY3314814 becomes commercially available in the host country of the patient. Safety data may be collected during this time period.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Discontinuation from Study Treatment

Discontinuation of the investigational product for abnormal liver tests **should be considered** by the investigator when a patient meets one of the following conditions after consultation with the Sponsor-designated medical monitor:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8X upper limit of normal (ULN)
- alanine aminotransferase or AST >5X ULN for more than 2 weeks
- alanine aminotransferase or AST >3X ULN and total bilirubin level (TBL) >2X ULN or prothrombin time >1.5X ULN
- alanine aminotransferase or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Alkaline phosphatase (ALP) elevations, if deemed of liver origin and drug-related as follows:
    - ALP >3X ULN
    - ALP >2.5X ULN and TBL >2X ULN
    - ALP >2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

In addition, patients **must** be discontinued from the investigational product in the following circumstances:

- Patient decision. The patient may discontinue treatment, without prejudice to further treatment, at any time.
- Adverse event or clinically significant laboratory value, ECG result, or vital sign measurement of such severity that, in the opinion of the investigator or medical monitor, continued treatment is not in the best interest of the patient
- Severe non-compliance to the study protocol that results in a safety concern, in the judgment of the investigator
- The patient, for any reason, requires a treatment with an excluded therapeutic agent and temporary discontinuation criteria can't be met (see Section 8.1.2)
- The patient develops a significant uncontrolled medical condition that in the opinion of the investigator after appropriate medical assessment, would pose an unacceptable risk to the patient if they were to continue receiving investigational product.

Patients who discontinue the investigational product early will have early discontinuation procedures performed as shown in the Schedule of Activities (Section 2).

8.1.2. Temporary Discontinuation from Study Treatment

Treatment can be temporarily discontinued (examples include short-term treatment using a prohibited drug, uncertain adverse event, hospitalization). Re-starting investigational product is based on 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 re-starting needs to be documented. If temporary discontinuation is due to an AE, it should be reported to the Sponsor-designated medical monitor.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Sponsor-designated medical monitor and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Sponsor-designated medical monitor to allow the inadvertently enrolled patient to continue in the study.

8.2. Discontinuation from the Study

Some possible reasons that may lead to permanent discontinuation include:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator decision: the investigator decides that the patient should be discontinued from the study
- Patient or study partner decision: requests to be withdrawn from the study
- An individual patient enrolled in the study may be discontinued based on a specific AE profile, as recommended by the Independent Data Monitoring Committee (IDMC), the medical monitor, and/or the sponsor Global Study Physician, in discussions with the Principal Investigator.

Patients who discontinue the study early will have early discontinuation procedures and follow-up procedures performed as shown in the Schedule of Activities (Section 2). Note: follow-up procedures are performed 4 to 6 weeks after last dose of investigational product.

8.3. Lost to Follow-Up

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

Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the patient will not be considered lost to follow-up.

Sponsor personnel will not be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study.

Appendix 5 provides a summary of the maximum number and volume of invasive samples to be taken during the study.

Unless otherwise stated in the subsections below, samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

9.1.1. Primary Outcome Efficacy Assessment

Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog; Rosen et al. 1984). Cognitive function will be assessed by using a 13-item version of ADAS-Cog. This version is composed of the original 11-item ADAS-Cog as well as Delayed Recall and Digit Cancellation items. Both items have been shown to be reliable and sensitive to a broad range of dementia severity and, therefore, provide a useful addition to the 11-item ADAS-Cog (Mohs et al. 1997). The maximum score for the ADAS-Cog_{13} is 85 points, with a lower score indicating better performance.

The ADAS-Cog has been designed specifically for the evaluation of the severity of major dysfunctions in the cognitive behavior characteristics of patients with AD. It has frequently been used in clinical studies in AD of mild-to-moderate severity and is recognized by regulatory authorities as a valid endpoint.

Administration of the ADAS-Cog-13 will be audio-recorded for quality-control and training purposes. Audio recordings will be centrally reviewed and monitored where permitted by local law.

9.1.2. Secondary Efficacy Assessments

Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory (ADCS-ADL; Galasko et al. 1997, 2004). The ADCS-ADL measures 6 basic and 17 instrumental activities of daily living and was specifically developed as a sensitive tool to track changes in functional performance in AD over time. The basic activities include self-care tasks such as eating, walking, toileting, bathing, and grooming. The instrumental activities are more complex skills that are required to successfully live independently and include shopping, keeping appointments, traveling outside of home, making a meal or snack, reading, and writing. These instrumental skills are often compromised in early AD.

For each activity on the ADCS-ADL, the score ranges from 0 to 78, with lower scores indicating greater impairment. The maximum basic items score (sum of individual basic item scores) is 22, and the maximum instrumental items score (sum of individual instrumental item scores) is 56 (Galasko et al. 2004).

Administration of the ADCS-ADL will be audio-recorded for quality-control and training purposes. Audio recordings will be centrally reviewed and monitored where permitted by local law.

Functional Assessment Questionnaire (FAQ; Pfeffer et al. 1982). The FAQ measures complex functional activities that may be impaired in AD (such as, ability to shop, cook, and pay bills). The FAQ is a study partner/ informant rating of the performance changes in 10 complex activities of daily living and has an overall score range of 0 to 30, with the higher score indicating greater impairment.

The 10 complex activities include: 1) manage finances, 2) complete forms, 3) shop, 4) perform games of skill or hobbies, 5) prepare hot beverages, 6) prepare a balanced meal, 7) follow current events, 8) attend to television programs, books or magazines, 9) remember appointments, and 10) travel out of the neighborhood.

Administration of the FAQ will be audio-recorded for quality-control and training purposes. Audio recordings will be centrally reviewed and monitored where permitted by local law.

Integrated Alzheimer's Disease Rating Scale (iADRS; Wessels et al. 2015) [calculated assessment, not a separately administered scale] is a composite that measures both cognition and function. The iADRS is a simple linear combination of scores from two well-established, therapeutically sensitive, widely accepted measures in AD, the ADAS-Cog_{13} and the instrumental activities within the ADCS-ADL (ADCS-iADL), measuring the core domains of AD. All items of these two scales are included without additional weighting of items, yielding face validity and ease of interpretation of the composite relative to its components.

The iADRS provides an overall measure of AD impairment (total score) and can also provide individual subscores for cognition and function based on standard, accepted instruments. The iADRS demonstrated acceptable psychometric properties (established through principal component analysis, estimation of the contributions of domain scores to the iADRS total score, and estimation of the contributions of individual item scores to the iADRS total score) and was effective in capturing disease progression and treatment effects (both beneficial and detrimental) across a broad range of the symptomatic disease spectrum – MCI/prodromal, mild AD dementia, and moderate AD dementia populations.

The iADRS score ranges from 0-141; with higher scores indicating greater impairment.

Clinical Dementia Rating (CDR; Hughes et al. 1982) is a global rating system widely used in clinical studies of AD as a measure of dementia severity and disease progression. The CDR ratings are based on a semi-structured and in-depth interview with both the patient and the patient's study partner. The CDR rates decline in cognition and its impact on functioning relative to the patient's own premorbid ability levels.

The CDR includes assessment of 6 independent domains (Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care). These domain ratings are also known as "box" scores and the Sum of Boxes (SB) score is derived by adding the individual box scores at a given time point. The CDR-SB is assessed on a scale from 0 to 18, with higher scores indicating greater impairment. The CDR global score is a composite score calculated using the Washington University CDR-assignment algorithm applied to the 6 individual domain box scores (Morris 1993). The memory domain is considered the primary category that drives the CDR global outcome, and all other domains are secondary. The CDR global score ranges from 0 to 3 (0 = no dementia, 0.5 = questionable dementia, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia). The CDR global score and memory box score will be used to determine patient eligibility.

Neuropsychiatric Inventory (NPI) is a well-validated clinical rating instrument designed specifically to assess a wide range of abnormal behaviors encountered in dementia patients (Cummings 1997; Cummings et al. 1994). The NPI is an informant-based interview that utilizes scripted questions to explore 12 different symptom domains: delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, night-time behavioral disturbances, and appetite and eating abnormalities. For each domain, the study partner is asked a screening question to determine whether the abnormal behavior has been present within the previous 4 weeks and represents a change in the patient since the onset of illness. If the behavior has been present, then a series of sub-questions are asked to obtain more detailed information about the specific features of the behavioral disturbance. The total NPI score has a possible range of 0 to 144, with higher scores indicating a greater degree of symptomatology.

The NPI also contains a Caregiver Distress Scale (NPI-D) that was designed to quantitate the distress experienced by caregivers as it relates specifically to the individual symptoms assessed in the patient by the NPI with a maximum score of 60.

Mini-Mental State Examination (MMSE; Folstein 1975) is a brief test used to screen for cognitive impairment. It is routinely used for estimating the severity of cognitive impairment and tracking cognitive changes in an individual over time. The MMSE assesses orientation to time and place, immediate and delayed recall of words, attention and calculation, language (naming, comprehension and repetition), and spatial ability (copying a figure). The maximum total score is 30, with a higher score indicating better cognitive performance. The range of permissible scores at screening for enrollment of patients is 20 to 26, inclusive.

Administration of the MMSE will be audio-recorded for quality-control and training purposes. Audio recordings will be centrally reviewed and monitored where permitted by local law.

9.1.3. Other/Exploratory Assessments

Eight-item Interview to Differentiate Aging and Dementia (AD8; Galvin et al. 2005). The Washington University Dementia Screening Test, also known as AD8, is completed by the study partner. This test is sensitive to detecting early cognitive changes and has a total score range of 0-8. This test is added to explore performance as a simple screening tool.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al. 1998; Duff et al. 2008). The RBANS is a collection of 12 subtests representing 5 neurocognitive domains: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. The raw scores from each subtest within a domain are converted to a summary score, or Index Score, for the domain by consulting normative data tables. The RBANS also provides an overall Index Score that summarizes the patient's overall level of performance on this measure.

Administration of the RBANS will be audio-recorded for quality-control and training purposes. Audio recordings will be centrally reviewed and monitored where permitted by local law.

EuroQoL-5D (EQ-5D; Kind 1996). The EQ-5D (proxy versions) is a standardized instrument used to measure overall health status and is applicable to a wide range of health conditions and treatments. It provides both a descriptive profile and a single index value for health status. The 5D in the name refers to the 5-dimensional classification system for health states used in the instrument. Each dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) has 3 levels of severity (no, some, and severe problems). Scores on individual dimensions are recorded, as is a total score that sums the individual dimension scores. A visual analog scale (VAS) also assesses the caregiver's impression of the patient's overall health state. Reliability and validity for use with an AD population have been demonstrated (Jönsson et al. 2006; Naglie et al. 2006). Scores can be converted into weighted health state preferences for quality-adjusted life year models.

Quality of Life in Alzheimer's Disease (QoL-AD; Logsdon et al. 2002; Thorgrimsen et al. 2003). The QoL-AD is a disease-specific measure of quality of life for an AD population. It includes 13 items, each rated on a 4-point scale. Summing the items provides an overall score to index the patient's quality of life. The QoL-AD is administered to the patient by a rater and asks the patient to provide ratings on mood, relationships, memory, finances, and so on. The patient's primary caregiver also is asked to complete the same measure. Reliability and validity in samples of AD patients and their caregivers have been demonstrated.

Resource Utilization in Dementia—Lite questionnaire (RUD-Lite; Wimo et al. 1998). The RUD-Lite is designed to assess the healthcare resource utilization of patients and their caregivers and to determine the level of formal and informal care attributable to AD. The data are collected through a structured interview. Information on both caregivers (caregiving time, work status) and patients (accommodation and healthcare resource utilization) is gathered from the baseline and final assessment interviews. Caregivers will be asked to provide data on time spent assisting patients' basic ADLs such as using the toilet, eating, dressing, grooming, walking, and bathing; assisting patients' instrumental ADLs such as shopping, cooking, housekeeping, laundry, transportation, taking medication, and managing finances; and providing supervision. The resource utilization quantified by the RUD-Lite can be used for calculating cost offsets and in cost-effectiveness models.

9.1.4. Appropriateness of Assessments

The ADAS-Cog is a widely accepted, validated clinical outcome measure. The scale reflects domains and abilities that are central to the characterization of an AD patient's deficits in a clinical setting and its items are linked to meaningful aspects of the lives of patients and caregivers. Furthermore, the scale has demonstrated its ability to detect treatment differences in the span of MCI and mild AD (Aronson et al. 2009; Orgogozo et al. 2004; Salloway 2004).

9.1.5. Order of Efficacy Assessments and Rater Qualifications

Assessments administered to the patient include the MMSE, ADAS-Cog_{13}, RBANS, QoL-AD and CDR. Assessments administered to the study partner include the AD8, CDR, FAQ, ADCS-ADL, NPI, EQ-5D, QoL-AD, and RUD-Lite.

Table 9.1 lists the relative sequencing of tests for both patient and study partner.

It is recommended that efficacy assessments be performed as the first activity at all specified visits. Additionally, it is recommended that, during these visits, cognitive and functional tests are performed in the sequence, if performed at the same visit, as shown in Table 9.1.

The CDR should always be administered to the study partner first and then to the patient; the study partner and patient must be interviewed separately. It is important to maintain the same test sequence at each visit for each patient throughout the study. Assessments should be scheduled to allow the cognitive testing to be performed at approximately the same time of the day (±4 hours) at all the visits to avoid the known circadian variation of cognitive performance (Higuchi et al. 2000). Patients and study partners should be assessed separately, because the presence of the other person may potentially contaminate the results of an assessment. When necessary, patients should be allowed a rest break between cognitive tests. Based on rater judgment, other nonstressful study procedures may be conducted during these breaks.

There should be at least two raters at each site. The sites can determine which rater does what scale. However, the ADAS-Cog_{13} should have a different rater than the rater who performs the CDR, ADCS-ADL, and FAQ for each patient. All other scales may be performed by any rater.

Table 9.1. Order of Test Administration for Patient and Study Partner

Patient	Study Partner
	Screening Visit
1. MMSE	1. AD8
2. ADAS-Cog_{13} (Rater 1)	2. CDR (Rater 2)
3. RBANS	
	Enrolled Visits
4. QoL-AD	1. FAQ (Rater 2)
5. CDR (Rater 2)	2. ADCS-ADL (Rater 2)
	3. CDR (Rater 2)
	4. NPI
	5. EQ-5D
	6. QoL-AD
	7. RUD-Lite

Abbreviations: AD8 = Eight-item Interview to Differentiate Aging and Dementia; ADAS-Cog_{13}=13-item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL=Alzheimer´s Disease Cooperative Study Activities of Daily Living Inventory; CDR = Clinical Dementia Rating; EQ-5D Proxy = 5-dimensional EuroQol quality of life scale; FAQ=Functional Activities Questionnaire; MMSE=Mini-Mental State Examination; NPI=Neuropsychiatric Inventory; QoL-AD = Quality of Life in Alzheimer's Disease; RBANS= Repeatable Battery for the Assessment of Neuropsychological Status; RUD-Lite=Resource Utilization in Dementia – Lite.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the Sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patients.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect or expected clinical progression is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the informed consent form (ICF) is signed, study site personnel will record via electronic case report form (eCRF) the occurrence and nature of each patient's preexisting conditions,

including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure and/or investigational product(s), via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, PET tracers, or a study procedure taking into account the disease, concomitant treatment(s), or concurrent pathologies/conditions.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, PET tracers and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to the Sponsor or its designee via eCRF clarifying, the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.

Although all AEs occurring after signing the ICF are recorded in the eCRF, SAE reporting begins after the patient has signed the ICF and has received investigational product or PET imaging. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product or PET imaging, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must alert the Sponsor or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process and subject should be consented to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify the Sponsor or its designee.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. The Sponsor has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

The Sponsor collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

Additional details regarding treatment of overdose are provided in the IB.

9.4. Safety

9.4.1. Electrocardiograms

For each patient, electrocardiograms (ECGs) should be collected according to the Schedule of Activities (Section 2). Electrocardiograms should be recorded according to the study specific recommendations included in the ECG central vendor's Manual of Operations for the study.

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 patient is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified.

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. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment should be reported to the Sponsor or its designee as an AE via eCRF per Section 9.2.

The Principal Investigator or physician delegate is responsible for reviewing all ECGs. Patient must meet eligibility criteria with respect to cardiac inclusion/exclusion criteria at the time of the screening.

Unscheduled ECGs may be obtained at the discretion of the investigator.

9.4.2. Vital Signs

For each patient, vital signs measurements, including temperature, should be conducted according to the Schedule of Activities (Section 2) at all office visits. Blood pressure and pulse will be measured supine and standing. Supine blood pressure and pulse rate should be taken after at least 5 minutes of supine rest. Standing blood pressure and pulse rate should be taken after 2 and 5 minutes in a standing position. Temperature will be recorded using an oral or tympanic thermometer.

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to the Sponsor or its designee as an AE via eCRF per Section 9.2.

9.4.3. Physical and Neurological Examinations

Complete physical examinations, brief physical exams, and complete neurological exams will be performed according to the Schedule of Activities (Section 2). The complete physical examination will include assessment of the following: general appearance; skin, head and neck; lymph nodes; thyroid; abdomen (bowel sounds, liver and spleen palpation); back (costovertebral angle tenderness); and musculoskeletal, cardiovascular, and respiratory systems. The brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (bowel sounds, liver and spleen palpation).

Complete neurological examinations will be conducted and will include a thorough assessment of gait, balance, coordination, cranial nerves, sensory and motor systems, and reflexes. A neurologist will be consulted in the event of significant new neurological findings.

Body weight and height will be recorded according to the Schedule of Activities (Section 2).

Any clinically significant changes on follow-up physical and neurological examinations should be reported to the Sponsor or its designee as an AE via eCRF per Section 9.2.

9.4.4. Laboratory Tests

For each patient, laboratory tests detailed in (Appendix 2) should be conducted according to the Schedule of Activities (Section 2).

Scheduled laboratory tests are performed by a central vendor. Any clinically significant findings from laboratory tests that result in a diagnosis and that occur should be reported to the Sponsor or its designee as an AE via eCRF per Section 9.2.

9.4.5. C-SSRS

Consistent with Food and Drug Administration (FDA) regulatory guidance (FDA 2012), any occurrence of suicide-related thoughts and behaviors will be assessed as indicated in the Schedule of Activities (Section 2). The Columbia Suicide Severity Rating Scale (C-SSRS) is a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the corresponding assessment period. The scale includes suggested questions to elicit the type of information needed to determine if a suicide-related thought or behavior occurred.

The C-SSRS is available in an adult's and a children's version. There is no version of the C-SSRS designed for use in a cognitively impaired population such as patients with AD; therefore, the children's version will be used. Terms captured by the use of the C-SSRS children's version can be mapped to Columbia Classification Algorithm for Suicide Assessment (Posner et al. 2007), to facilitate future pooling of data.

The first time the scale is administered in this study (at Visit 2), the C-SSRS "Baseline/Screening" version will be used, and the findings will constitute the baseline assessment. The C-SSRS "Since Last Visit" version will be used for all subsequent assessments. The C-SSRS will be administered to the patient with the caregiver/study informant present, after the cognitive and functional assessments. Responses from both the caregiver/study informant and patient will be considered when administering the scale. If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided.

The Lilly Self-Harm Supplement should be completed every time the C-SSRS is administered. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

Any clinically significant findings from the C-SSRS should be reported to the Sponsor or its designee as an AE via eCRF per Section 9.2.

9.4.6. Magnetic Resonance Imaging (Safety)

Magnetic resonance imaging of the brain will be performed according to the Schedule of Activities (Section 2) and as clinically indicated. This technology will be used to check for evidence of Amyloid Related Imaging Abnormality (ARIA-Hemmorhage [ARIA-H] and ARIA-Edema [AIRA-E]). ARIA-Edema is associated with immunotherapies; no association is currently known for LY3314814. See Section 9.4.9.4 regarding vasogenic edema for additional information. The MRI data will also be used to calculate brain volumes as a potential efficacy biomarker.

The MRI scans will be sent for analysis to a centralized MRI vendor designated by the Sponsor. The scans will be reviewed by the investigator or qualified designee for immediate patient management. Study eligibility will be determined by central vendor read. Any clinically significant findings from MRI that result in a diagnosis should be reported to the Sponsor or its designee as either a pre-existing condition or AE via eCRF per Section 9.2. Specific analyses of the scans including assessments of ARIA-H and ARIA-E and calculations of brain volumes will subsequently be interpreted by the centralized MRI vendor for data analysis and report-writing purposes. Results of centrally read MRIs regarding patient care/safety will be reported back to sites even though there was a local read.

9.4.7. Eye examination

A comprehensive eye examination, to include corrected visual acuity, intraocular pressure, a slit lamp examination, and a dilated fundus examination (dilation only performed in patients without contraindication to mydriatics), will be performed at the times shown in the Schedule of Activities (Section 2). The eye examinations must be reviewed and/or performed by an optometrist or ophthalmologist, preferably using the same optometrist or ophthalmologist for each patient's visit. Patients who complain of vision disturbance during the clinical trial should be referred to the optometrist or ophthalmologist for unscheduled evaluation.

Any clinically significant findings that result in a diagnosis should be recorded to the Sponsor or its designee as a pre-existing condition or AE via eCRF per Section 9.2. The principal investigator will make all final determinations of AEs in consultation with performing eye examiner.

9.4.8. Skin examination

A complete skin examination will be performed at the times shown in the Schedule of Activities (Section 2).

All skin examinations must be reviewed and/or performed by a dermatologist who will inspect the patient's unclothed full body using a UV light. The initial examination will include the Fitzpatrick skin-type classification scale. The follow-up skin examinations will preferably be completed for a given patient by the same dermatologist who conducted the initial examination.

At each examination, abnormal hypopigmentation will be assessed by location, percentage of body surface area involvement, degree (partial/decreased pigmentation to complete depigmentation), and other findings in or around the hypopigmented area (such as redness or induration). A static physician's global assessment will be used to determine the patient's overall hypopigmentation severity at a given timepoint using a visual analog scale (VAS) ranging from 0 to 100. In addition, patients noted to have evidence of hypopigmentation will be asked to record how bothersome they find the hypopigmentation on a VAS ranging from 0 to 100. Skin photographs may be taken as appropriate for generating supporting documentation, but not for the purpose of primary clinical dermatologic evaluation or for data generation or analysis. A punch biopsy may be obtained at the discretion of the dermatologist.

Any clinically significant findings that result in a diagnosis should be recorded to the Sponsor or its designee as a pre-existing condition or AE via eCRF per Section 9.2. The principal investigator will make all final determinations of AEs in consultation with the dermatologist.

9.4.9. Safety Monitoring

The Sponsor will periodically review evolving aggregate safety data within the study by appropriate methods.

If a study patient/subject experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, hepatic clinical and laboratory monitoring should be initiated by the investigator. In the presence of Gilbert syndrome, isolated elevation of bilirubin with normal ALT, AST, and ALP may not require additional evaluation. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Sponsor-designated medical monitor regarding collection of specific recommended clinical information and follow-up laboratory tests. Additional hepatic eCRF should be completed for these patients as information becomes available. See Appendix 4.

9.4.9.1. Adverse Events of Special Interest

Adverse events of special interest will include:

- Adverse eye effects including retina (Section 9.4.7)
- Adverse skin effects including rash (Section 9.4.9.3) and hypopigmentation (Section 9.4.8)
- Peripheral nervous system, central nervous system and muscle effects
- Liver toxicity (Section 9.4.9 and Section 8.1.1)
- Cardiovascular (CV)-type events (including, but not limited to, orthostatic hypotension and QT prolongation) (Section 9.4.9.2)

The topics listed above, as well as new 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 Clinical Study Report in accordance with the Statistical Analysis Plan (SAP).

9.4.9.2. MACE Adjudication

Alzheimer's disease occurs mainly in elderly people, who may have established CV disease or CV risk factors and constitute a population of patients at increased risk of CV events. Serious CV events, as well as particular arrhythmic events related to QTcF prolongation, are therefore of potential special interest. Serious adverse events that, according to the investigator, may be CV events of the major adverse CV event (MACE) type (myocardial infarction, stroke, or CV death) or may be potential QT prolongation-related arrhythmic events, such as, syncope, ventricular tachycardia/torsades des pointes/fibrillation, or cardiac arrest, will be carefully documented and sent for adjudication. The events will be blindly evaluated by external independent consultants and adjudicated as MACE events per a separate adjudication charter.

9.4.9.3. Rash

In the event a patient experiences a suspected drug-induced rash, the following procedures should be followed:

- The patient should be referred to a dermatologist for an expert opinion.
- A photograph of the rash should be taken.
- A blood sample should be drawn for PK analysis.
- A punch biopsy may be obtained at the discretion of the dermatologist.

If treatment is discontinued due to a suspected drug-induced rash, the Sponsor-designated medical monitor should be notified as soon as possible, even if the rash did not meet the definition of an SAE.

9.4.9.4. Vasogenic Edema

If a patient develops symptoms suggestive of vasogenic edema, such as headache, confusion, gait disturbance, or visual disturbance, these should be recorded as AEs and an MRI should be obtained. Study treatment should be discontinued if clinically significant symptomatic vasogenic edema, clinically significant symptomatic superficial siderosis, or clinically significant symptomatic incident microhemorrhage is seen. Following the study treatment discontinuation, the MRI scan should be repeated within 4 weeks to evaluate the status of the finding and then performed every 4 to 6 weeks (or as clinically indicated) until the finding resolves or stabilizes. Treatment with high-dose dexamethasone is to be considered, should symptoms be severe.

9.4.9.5. IDMC

This study will use an IDMC (an independent, external advisory group for this study formed to protect the integrity of data) to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in the study, to ensure the integrity of the blinded nature of the study, and to oversee any interim analyses (see Section 10.3.7). The IDMC details and structure will be laid out in its charter. In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the IDMC can conduct additional analyses of the safety data.

9.5. Pharmacokinetics

At the visits specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine the plasma concentrations of LY3314814 and its metabolite AZ13569724. At these visits, the date and time of dosing on the visit day, as well as the date and time of the previous two doses administered will be recorded. Additionally, it will be recorded if the patient consumed a meal within 2 hours before or after dose administration on the day of the study visit. The actual date and time of each sampling will be recorded.

Specific details regarding each of the visits are as follows:

- Visit 4: A phone call will be made 1 day before clinic visit to remind patients to hold the morning dose of study treatment on the day of the visit and bring the dose to the clinic. A blood sample should be collected at arrival, and again at the end of the visit. The patient is to receive the morning dose after the first sample.
- Visit 5: A phone call will be made 2 days before the clinic visit to remind patients to 1) hold the morning dose of study treatment on the day prior to the visit and then take that dose late in the afternoon (at least 14 hours prior to the clinic visit) and 2) hold the morning dose of study treatment on the day of the visit and bring that dose to the clinic. The blood sample may be collected at any time during the visit, and the dose may be administered after the sample is collected.
- Visit 7: A phone call will be made 1 day before clinic visit to remind patients to hold the morning dose of study treatment on the day of the visit and bring the dose to the clinic. A blood sample should be collected at arrival, and again at the end of the visit. Patient is to receive the morning dose after the first sample.
- Visit 10: A phone call will be made 1 day before clinic visit to remind patients to take the morning dose of study treatment as scheduled on the day of the visit, before arriving at the clinic. A blood sample should be collected at the end of the visit.
- Visit 11: A phone call will be made 1 day before clinic visit to remind patients to hold the morning dose of study treatment on the day of the visit and bring that dose to the clinic. After cognitive testing is complete, a blood sample should be taken, immediately after which the patient should receive a dose of study treatment. A second blood sample is to be collected 30-45 minutes after dose administration.
- Visit 15: A blood sample will be collected from only those subjects receiving a lumbar puncture. In these patients, a blood sample will be collected at approximately the same time as the lumbar puncture. There are no special instructions for dosing at this visit.

If the patient fails to follow the dosing instructions, blood samples are still to be collected according to the Schedule of Activities (Section 2) and as described above. On those visits where the dose is to be administered at the site, if the patient fails to follow this instruction and is dosed prior to sample collection, an additional dose will not be administered at the visit.

Up to three additional unscheduled PK collections may occur in the event of rash, as part of the assessment of hepatic laboratory abnormalities, or as determined to be warranted by the sponsor.

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

Post-baseline CSF samples are to be analyzed for determination of LY3314814 and AZ13569724 concentrations. See Section 9.8.1 for additional details around the collection of CSF samples.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last patient visit for the study. During this time, samples

remaining after the bioanalyses may be used for exploratory analyses such as metabolism and/or protein binding work.

9.6. Pharmacodynamics

The peripheral dose-dependent PD activity of LY3314814 and placebo administration will be evaluated by analysis of plasma $A\beta_{1-40}$ and $A\beta_{1-42}$ as measured using validated immunoassays. These plasma based biomarkers will provide an assessment of target engagement.

Bioanalytical samples collected to measure plasma $A\beta_{1-40}$ and $A\beta_{1-42}$ will be identified by the patient number (coded) and retained for a maximum of 1 year following last patient visit for the study at a facility selected by the Sponsor or its designee.

9.7. Genetics

9.7.1. Apolipoprotein E Genotyping

Apolipoprotein E (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 in the Schedule of Activities (Section 2). Neither patients 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 violation if country-specific regulations prohibit the testing of genetic material or transportation of such material outside of the country.

9.7.2. Whole Blood Samples for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2) 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 LY3314814 and to investigate genetic variants thought to play a role in AD and neurodegeneration. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/investigational review boards (IRBs) impose shorter time limits, at a facility selected by the Sponsor or its designee. 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 LY3314814 or after LY3314814 become(s) 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.

9.8. Biomarkers and Imaging

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient 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 (DNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

Serum, plasma, CSF, and whole blood RNA samples for non-pharmacogenetic biomarker research and MRI and PET images will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples and images will be used for research on the drug target, disease process, variable response to LY3314814, pathways associated with AD and neurodegeneration, mechanism of action of LY3314814, and/or research method or in validating diagnostic tools or assay(s) related to AD and neurodegeneration.

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

Samples and images will be retained for a maximum 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits, at a facility selected by the Sponsor or its designee. 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 LY3314814 or after LY3314814 become(s) commercially available.

9.8.1. Cerebrospinal fluid biomarkers

Cerebrospinal fluid samples are collected for analysis of concentrations of $A\beta_{1-40}$, $A\beta_{1-42}$, total tau, phosphorylated tau, and exploratory biomarkers (Schedule of Activities, Section 2). If a post-baseline CSF sample cannot be obtained because of procedural complications, patient issues, or patient request; or if it is not obtained in certain countries, it will not be considered a protocol violation.

Lumbar punctures should be scheduled at approximately the same time of the day (±4 hours) at all visits to avoid the known circadian variation of CSF amyloid levels (Lucey and Bateman 2014). Cerebrospinal fluid samples will be collected by insertion of an atraumatic (preferable) spinal needle between vertebrae L3 and L5 (Vanderstichele et al. 2012). Before performing the lumbar puncture procedure, the physician must take into account the overall assessment of the patient.

Cerebrospinal fluid $A\beta_{1-40}$ and $A\beta_{1-42}$ are biomarkers for BACE inhibition that enable direct measure of the central PD of LY3314814.

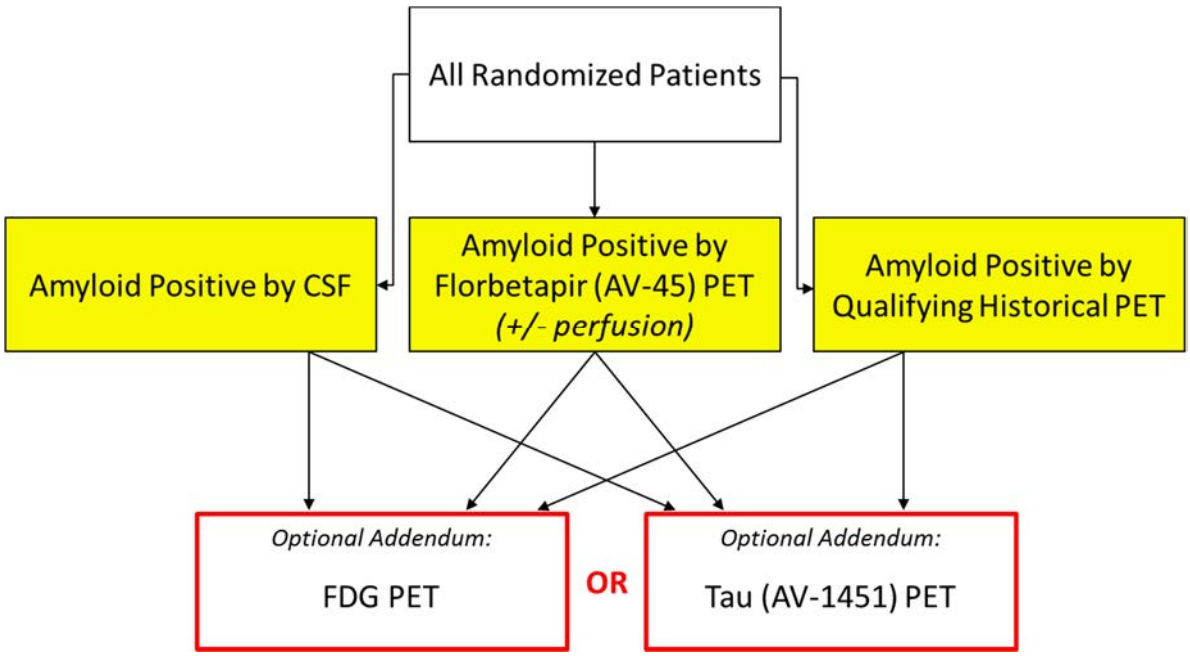
Cerebrospinal fluid tau and phosphorylated tau concentrations are elevated in patients with AD. Elevations in concentrations of tau, as well as specific phosphorylated tau species, are thought to be markers for progressive neurodegeneration in AD. Accordingly, reductions from baseline in concentrations of CSF tau in patients who receive LY3314814 compared with patients who receive placebo may be indicative of reduced neuronal loss in LY3314814-treated patients.

Other CSF metabolites and/or protein species, including processed forms of APP such as sAPPβ, inflammatory biomarkers, other recognized or as yet unrecognized biomarkers, and, if appropriate, proteomics assessments may be examined. Biochemical signatures may help to explain differences in efficacy, safety, or tolerability and/or PK/PD related to LY3314814 treatment.

Detailed sample collection and handling procedures are provided in the Laboratory Manual.

9.8.2. Imaging biomarkers

A flow diagram of the imaging biomarkers and optional addenda is depicted in Figure 9.1.



Abbreviations: CSF = cerebrospinal fluid; FDG = fluorodeoxyglucose; PET = Positron emission tomography.
Note: Red boxes denote optional FDG PET or ^{18}F-AV-1451 Tau PET addenda

Figure 9.1. Flow diagram of optional addenda.

9.8.2.1. Florbetapir PET (Positron emission tomography)

Florbetapir amyloid PET is one method used to evaluate eligibility for study. Historical amyloid PET scans may be submitted for study eligibility with central reader confirmation of amyloid positivity. Florbetapir and historical amyloid PET results for patient eligibility will indicate "eligible" or "non-eligible". Amyloid PET images from those patients who do not meet

screening amyloid burden criteria for enrollment will be retained for future research to understand factors influencing screen failures.

A total of 3 florbetapir scans will be performed. At each florbetapir PET scanning visit, the patient will receive a single IV administration of approximately 370 MBq (10 mCi) of 18F florbetapir, and will be scanned twice. First, a scan of approximately 6 minutes duration will be taken immediately following injection of the tracer. This scan will capture the blood flow to the brain (perfusion florbetapir scan). Second, starting approximately 50 minutes after the tracer injection, a scan lasting approximately 10 minutes will be acquired to measure amyloid burden (florbetapir amyloid scan). The primary quantitative florbetapir PET outcomes will be regional estimate of amyloid burden (Standardized Uptake Value Ratio [SUVr], see Section 10.3.3.6 for details) and regional cerebral blood flow (rCBF) derived from the florbetapir perfusion scan (see Section 10.3.3.6.5 for details).

Florbetapir PET scanning will be conducted under the management of a central PET vendor. The central PET vendor will provide visual interpretation and quantitative analysis of all PET imaging data.

The details of patient preparation, florbetapir dose ordering and injection, patient positioning, image acquisition, and scan submission will be documented in the central PET vendor's technical operations manual. The details of scanner qualification, image acquisition and reconstruction, analysis and reader training will be documented in the central PET vendor's image review charter.

9.8.2.2. Magnetic Resonance Imaging (Efficacy)

The following volumetric measures will be derived from the MRI scans using automated methods: hippocampus volume, hippocampus atrophy, whole brain volume, whole brain atrophy, ventricular volume, ventricular enlargement, entorhinal cortex volume, entorhinal cortex atrophy, temporal lobe volumes, and temporal lobe atrophy.

MRI images from those patients who do not meet screening amyloid burden criteria for enrollment will be retained for future research to understand factors influencing screen failures.

Details of the qualification, imaging, processing and analysis will be contained in the MRI vendor technical operations manual.

9.9. Health Economics

The self-reported questionnaires will be administered according to the Schedule of Activities (Section 2) in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

Health economic and outcomes data capture will focus on the assessment of resource utilization and health-related quality of life. Resource utilization associated with direct medical resources, caregiver informal care and patient social care will be collected via the RUD-Lite (Wimo et al. 1998). In addition, health-related quality of life will be captured with the EQ-5D and QoL-AD. See Section 9.1.3 for full scale descriptions.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 1899 patients may be enrolled/randomized in order that 1424 patients complete the Placebo-Controlled period of the study.

The sample size has been calculated to provide 90% power to detect a treatment difference in a functional secondary outcome, that is, change in ADCS-iADL at 78 weeks. Based on estimates of treatment change and standard deviation from the mild ApoE4 carriers (ApoE4 used as a surrogate for amyloid positivity) in pooled solanezumab studies NCT00905372 (H8A-MC-LZAM [LZAM]) and NCT00904683 (Study H8A-MC-LZAN [LZAN]), an expected mean change (SD) in ADCS-iADL score is 2.07 (9.78), which equates to an effect size of 0.212. Using the R package 'pwr' and accompanying function 'power.t.test', 554 completing patients per arm are needed to provide 90% power with α=0.025. Assuming a 25% dropout rate and a 50% information rate for dropouts, 633 (554/(1-0.25%*50%)) patients will need to be randomized per arm (633 in combined placebo arms during the Placebo-Controlled period). This equates to a total randomized sample size of 1899.

This calculated sample size provides greater than 90% power to evaluate the primary outcome for the Placebo-Controlled period. Based on estimates of treatment change and standard deviation from the mild ApoE4 carriers in pooled solanezumab studies LZAM/LZAN, an expected mean change (SD) in ADAS-Cog_{13} score is 2.91 (10.84) which equates to an effect size of 0.269. Using the R package 'pwr' and accompanying function 'power.t.test', 633 patients randomized per arm will provide 99.4% power for this analysis.

Using the three stage hypothesis testing approach to delayed start analysis as outlined in Liu-Siefert and colleagues (2015b), this sample size will provide approximately 80% power for each dose when all patients have the opportunity to complete the 6 month time point at an alpha level of 0.1. At the 18 month time point of the Delayed-Start period, this sample size will provide approximately 50% power.

These powering results are based on solanezumab Delayed-Start results of mild, ApoE4 carriers. Treatment differences at the end of the Placebo-Controlled and Delayed-Start periods and the corresponding variance and covariance estimates were used to calculate the power empirically. For the 6 month time point, the assumed early discontinuation (EDC) rate was 30%; for 18 months, 40%, over the entire 3 year study. These EDC assumptions were used to adjust the randomized sample sizes using the following formula:

$$\text{Effective Sample Size} = (\text{Randomized Sample Size}) * (1 - 0.50*\text{EDC})$$

The effective sample size assumes that EDC patients will contribute half the information that completing patients contribute. The effective sample sizes for the 6 month power calculation were 531 and 266, early-start arm and delayed-start arm, respectively; for 18 months, 500 and 250, early-start arm and delayed-start arm, respectively.

The R package 'pwr' and accompanying function 'pwr.t2n.test' were used to calculate the power estimates. To be consistent with Liu-Seifert and colleagues (2015b), sig.level was set equal to 0.1 and alternative was set equal to "greater".

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Entered	All participants who sign informed consent
Randomized	All entered patients who are randomized to study treatment. Participants who had no post randomization efficacy measure for the parameter being analyzed will be excluded.
Evaluable (Intention-to-treat [ITT] analysis)	All randomized patients with a baseline and at least one post-baseline scale result. The ITT principle asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients 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.
Safety	All randomized participants who take at least 1 dose of double-blind study treatment. Participants will be analyzed according to the treatment group they were randomized to.
Per-protocol	All subjects in the Evaluable population who also: • signed the inform consent form • had an assessment of the primary endpoint at each scheduled visit completed • had no violations of inclusion/exclusion criteria • had no study dosing algorithm violation (such as if subjects randomized to treatment A were given treatment B or subjects randomized to treatment A never received the assigned study drug) • had no unqualified raters and no raters with substantial scoring errors for the primary measure • was not considered non-compliant with regard to study drug

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of the Sponsor.

Efficacy analyses will be conducted on the Evaluable analysis set. This set includes all data from all randomized patients according to the treatment the patients were assigned and with a baseline and at least one post-baseline scale result.

For treatment group comparisons of the Placebo-Controlled phase of the study the two placebo treatment groups (PLA-LY20 and PLA-LY50) will be pooled to form one placebo-treated control group. This group will be labelled as the placebo treatment group (PLA).

Unless otherwise noted, all pairwise tests of treatment effects in the Placebo-Controlled period will be conducted at a 2-sided alpha level of 0.025; 2-sided confidence intervals (CIs) will be displayed with a 97.5% confidence interval. All tests of interactions between treatments and other factors will be conducted at an alpha level of 0.05. For MMRM models, observations collected at nonscheduled visits will not be included in the analyses (Andersen and Millen 2013). For analyses using last observation carried forward (LOCF), the last nonmissing post-baseline observation (scheduled or unscheduled) will be used to calculate change from baseline.

Investigators with fewer than 6 evaluable patients will be pooled for statistical analysis purposes. All investigative sites with fewer than 6 evaluable patients on the primary endpoint measure will be pooled together within each country and considered a single site for analysis. If this results in a pooled site still having fewer than 6 evaluable patients, this site will be pooled together with the next smallest investigative site, if one exists, in that country; otherwise, no further pooling is needed. These pooled investigative sites will be used for any analysis that has investigative site as a fixed effect in the model. The actual investigative site numbers will be included in the listings.

If any of the individual items for ADAS-Cog or ADCS-ADL are missing or unknown, every effort will be made to obtain the score for the missing item or items.

For ADAS-Cog_{13}, if <30% (4 or fewer of a total of 13) of the items are missing, the total score (maximum = 85) will be imputed as follows: The total from remaining items will be multiplied by a factor that includes the maximum score for the missing items. For example, if the first item, "Word-Recall Task," which ranges from a score of 0 through 10 (maximum = 10), is missing, and the second item "Commands," which ranges from a score of 0 to 5 (maximum = 5), is missing, then the multiplication factor = 85/(85 - [10 + 5]) = 85/70 = 1.21. Thus, the total score for this example will be the sum of the remaining 11 items multiplied by 1.21. The imputed number will be rounded up to the nearest integer. If more than 4 items are missing, the total score for ADAS-Cog_{13} at that visit will be considered missing.

For the ADCS-iADL, if <30% of the items are missing, the total score will be imputed. The sum of the nonmissing items will be prorated to the sum of total items. The imputed number will be rounded up to the nearest integer. If the nearest integer is greater than the maximum possible score, the imputed score will be equal to the maximum score. If >30% of the items are missing, the total score for ADCS-iADL at that visit will be considered missing.

The same imputation technique will be applied to the ADCS-ADL total score. Note that, depending on the specific item responses that are missing, it is possible to have an imputed total score for both the ADCS-iADL and the ADCS-ADL, an imputed total score for one but not the other, or both total scores missing.

The same imputation technique will be applied to the CDR-SB. If only 1 box (of 6) of the CDR is missing, the sum of the boxes will be imputed by prorating the sum from the other 5 boxes. If the score from more than 1 box is not available, the CDR-SB at that visit will be considered missing.

For all other scales, if any item is missing, any total or sum involving that item will be considered missing.

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 clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

The primary objective of the study and the Placebo-Controlled period will be assessed using a MMRM analysis of the ADAS-Cog_{13}, in which the specific hypothesis is that the decline at the end of the Placebo-Controlled period for at least one dose of LY3314814 will be significantly less than that for placebo.

The primary analysis of the Delayed-Start period is to assess if there is a significant difference in mean change from baseline on the ADAS-Cog_{13} at the 6 month time point of the Delayed-Start period and to evaluate whether a sufficient amount of the treatment benefit at the end of the Placebo-Controlled period is retained at the 6 month time point of the Delayed-Start period.

Patients who meet all criteria for enrollment will be assigned a study (patient) number and randomized to double-blind treatment at Visit 2. For between-group comparability, patients will be randomized by site. Assignment to treatment groups will be determined by a computer generated random sequence using an IxRS.

The IxRS will be used to assign a dosing regimen to each patient. Site personnel will confirm that they have located the correct package by entering a confirmation number found on the label into the IxRS.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

All patients 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.

As is typical for most studies, the following analyses of patient disposition will be conducted. The reasons for discontinuation will be collected when the patient's participation in the study ends and will be summarized by treatment group for all randomized subjects from each study. The percentage of subjects discontinuing from each treatment group will be compared between groups using Fisher's exact test. The median time to discontinuation for these reasons will also be compared between treatment groups using the Kaplan-Meier product limit estimator. The comparisons using both the Fisher's exact test and the Kaplan-Meier product limit estimator will be done for the overall percentage of patients who discontinue and also for select specific reasons for discontinuation.

The percentage of subjects discontinuing from each treatment group will be compared by reason for discontinuation using Fisher's exact test.

10.3.2.2. Patient Characteristics

The patient's age, gender, race, height, body weight, body mass index (BMI) (weight (kg) / [height (m)]2), tobacco use, alcohol use, caffeine use, years of education, work status, time since onset of first AD symptoms, time since diagnosis, CDR global score at Visit 1, MMSE at Visit 1, apolipoprotein E4 (APOE4) carrier status (carrier [ε2/ε4, ε3/ε4, ε4/ε4], noncarrier [ε3/ε3, ε2/ε2, ε2/ε3]), APOE4 genotype (ε2/ε4, ε3/ε4, ε4/ε4, no ε4), having 1 or more first degree relatives with AD, and acetylcholinesterase inhibitor (AChEI) and/or memantine use at baseline will be recorded.

Baseline characteristics will be summarized for the randomized and per-protocol populations by treatment group and overall. 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.

10.3.2.3. 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 AChEI/memantine medications. Medications will be coded using the World Health Organization (WHO) drug dictionary.

10.3.2.4. Treatment Compliance

The proportion of patients who are significantly noncompliant as noted in Section 7.6 of this protocol will be summarized and compared among all treatment groups using Fisher's exact test.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Outcome Analyses

Unless otherwise noted, all tests of treatment effects for the Placebo-Controlled period will be conducted at a 2-sided alpha level of 0.025. All tests of interactions between treatment and other factors will be conducted at an alpha level of 0.05. For MMRM models, observations collected at nonscheduled visits will not be included in the analyses. The primary and secondary efficacy measures will be analyzed using the evaluable/intention-to-treat (ITT) efficacy population unless otherwise specified. In addition, the ADAS-Cog_{13}, iADRS and the ADCS-iADL will be analyzed using the per-protocol population to verify the robustness of the results. See additional details in Section 10.2.

The primary objective of this study and of the Placebo-Controlled period is to test the hypothesis that at least one dose of LY3314814 will slow the clinical decline of AD compared with placebo

in patients with mild AD dementia. This will be assessed using an MMRM analysis of the ADAS-Cog_{13} in patients with mild AD dementia at baseline, in which the specific hypothesis is that the decline from baseline at the end of the Placebo-Controlled period (78 weeks) for at least one dose of LY3314814 will be significantly less than that for placebo.

The change from baseline score on the ADAS-Cog_{13} at each scheduled post-baseline visit (according to the Study Schedule) during the Placebo-Controlled period will be the dependent variable. The model for the fixed effects will include terms for 8 effects: baseline score, pooled investigator, treatment, visit, treatment-by-visit interaction, baseline-by-visit interaction, concomitant AChEI and/or memantine use at baseline (yes/no), and age at baseline. Visit will be considered a categorical variable with values equal to the visit numbers at which the scales were assessed.

The null hypothesis is that the contrast between both LY3314814 dose groups versus placebo at the last visit equals zero. An unstructured covariance matrix will be used to model the within-subject variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the following tests will be used in sequence: heterogeneous Toeplitz covariance structure, heterogeneous autoregressive covariance structure, heterogeneous compound symmetry covariance structure, and compound symmetry covariance structure.

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

10.3.3.2. Delayed-Start

Additional data beyond the 78 week Placebo-Controlled period are generated from the Delayed-Start study period. The primary analysis of the Delayed-Start study period is to test for differences in disease progression between treatment groups from the end of the Placebo-Controlled study period to the 6 month time point in the Delayed-Start study period. Comparisons of the ADAS-Cog_{13} are made between those patients who were started early on LY3314814 in the Placebo-Controlled period versus those who started LY3314814 in the Delayed-Start period. The analysis will proceed following the methodology described in Liu-Seifert and colleagues (2015b).

The primary analysis of the Delayed Start period will be done using all available data up to the 6 month time point at the time of the last patient visit in the Placebo-Controlled period. The MMRM model will include terms for 8 independent fixed effects: baseline score, pooled investigator, treatment, visit, treatment-by-visit interaction, baseline-by-visit interaction, concomitant AChEI and/or memantine use at baseline (yes or no), and age at baseline. Visit will be considered a categorical variable with values equal to the visit numbers at which the scales were assessed.

The time points beyond the primary analysis at 6 months of the Delayed-Start period will be analyzed upon last patient visit for Visit 30 to determine the robustness of early treatment over the full 18-month delayed-period following the same methodology.

10.3.3.3. Secondary Analyses

10.3.3.3.1. Gatekeeping strategy

A gatekeeping strategy will be used in Study AZET for testing hypotheses of outcomes to protect against type I error of falsely rejecting a null hypothesis. Gatekeeping will use a prespecified analysis plan that employs Bretz' graphical approach to provide strong control of the study wise Type I error rate for the primary and key secondary hypotheses in the Placebo-Controlled period at level $\alpha = 0.05$ (Bretz et al. 2009; Bretz et al. 2011). The final designations of the vector of hypothesis weights and the matrix of transition weights (or alpha propagation weights) are subject to optimization and, thus, will be prespecified in the study SAP prior to database lock. If any changes to the gatekeeping strategy are deemed necessary, the final gatekeeping strategy will be prespecified in the SAP before study database lock.

10.3.3.3.2. Secondary MMRM Efficacy Analyses – Placebo-Controlled period

A secondary objective of the Placebo-Controlled period is to test the hypothesis that at least one dose of LY3314814 will slow the functional decline (ADCS-iADL and/or FAQ) and/or cognitive/functional outcomes (CDR-SB and/or iADRS) of AD compared with placebo in patients with mild AD. This will be assessed using MMRM analyses, in which the specific hypothesis is that the functional decline from baseline at the end of the treatment period (78 weeks) for at least one dose of LY3314814 will be significantly less than that for placebo. The MMRM model used in the primary analysis will also be employed for these key secondary analyses.

Similar to the primary analysis, each of the additional secondary efficacy outcomes will be assessed using an MMRM analysis. These secondary efficacy outcomes include MMSE and NPI. For each secondary efficacy measure, the change from baseline score at each scheduled postbaseline visit (according to the Study Schedule) during the Placebo-Controlled period will be analyzed using the same MMRM model described for the primary analysis.

An additional MMRM analysis, termed a slopes analysis, will be conducted examining the change from baseline score on the ADAS-Cog_{13}, ADCS-iADL, and FAQ at each scheduled postbaseline visit. In contrast to the primary analyses which considered visit (time) as a categorical variable, time from randomization in this analysis will be treated as a continuous variable. The model for the fixed effects will include baseline score, pooled investigator, treatment, time, treatment-by-time interaction, concomitant AChEI and/or memantine use at baseline (yes/no), and age at baseline. The treatment-by-time interaction term will be examined to assess whether each LY3314814 treatment group and placebo have differing slopes in terms of ADAS-Cog_{13}, ADCS-iADL, or FAQ progression. The effect of a quadratic term for time (and its associated interaction with treatment) on the model will also be examined.

10.3.3.4. Prolong Time in the Current Disease State

Time in the current disease state, defined as the time until progression to the next disease state as measured by the CDR global score, will be analyzed for the Placebo-Controlled period using time-to-event techniques. For patients enrolled with a CDR global score of 0.5, progression is defined as a CDR global score of 1 or greater. For patients enrolled with a CDR global score of

1, progression is defined as a CDR global score of 2 or greater. Kaplan-Meier methodology will be used to estimate median time-to-event for each treatment group and Kaplan-Meier curves by treatment group will be presented. A stratified log-rank test will be used to test the hypothesis of equal survival curves between the LY3314814 treatment groups and the placebo group.

10.3.3.5. Secondary Analyses – Delayed-Start period

The methods used for the primary analysis of the Delayed-Start period will be used to explore the durability of effect by assessing whether there is a significant difference in mean change from baseline on ADAS-Cog_{13} at later time points in the Delayed-Start period.

The Delayed-Start methodology will also be used to examine additional clinical outcome measures, including MMSE, iADRS, ADCS-iADL, and FAQ. Further details on these secondary analyses will be provided in the SAP.

10.3.3.6. Analysis of Biomarkers

10.3.3.6.1. Analysis of Plasma Aβ

To evaluate the change in plasma Aβ analytes (including assayed plasma $A\beta_{1-40}$ and $A\beta_{1-42}$) after treatment, an MMRM will be used to compare change from baseline to 52 and 71 weeks. This analysis will be done separately for each plasma Aβ parameter. The model for the fixed effects will include terms for the following independent effects: baseline plasma Aβ, treatment, visit, and treatment-by-visit interaction. Visit will be considered a categorical variable with values equal to the visit numbers at which plasma Aβ is assessed. The null hypothesis is that the difference in least squares means (LSM) between the LY3314814 dose groups and placebo equal zero. A similar analysis will be performed for completers.

To assess the effects of various demographic and baseline characteristics, subgroup analyses of the change from baseline to 52 and 71 weeks in plasma Aβ analytes will be performed. Two subgroups will be included for this analysis, provided there are at least 50 subjects for all categories of a subgroup in each treatment group: (1) ApoE4 carrier status (carrier [ε2/ε4, ε3/ε4, ε4/ε4], noncarrier [ε3/ε3, ε2/ε2, ε3/ε2]) and (2) ApoE4 genotype (ε2/ε4, ε3/ε4, ε4/ε4, no ε4). These analyses will be carried out using an MMRM including the following independent effects: baseline plasma Aβ analyte, treatment, visit, and treatment-by-visit interaction as well as the subgroup of interest and the subgroup-by-treatment, visit-by-subgroup and treatment-by-visit-by-subgroup interactions.

To assess the relationship of plasma Aβ with cognition and function with treatment, Spearman's rank correlation coefficient will be obtained on change in plasma Aβ from baseline to Week 71 and with change from baseline to Week 78 for ADAS-Cog_{13}, ADCS-iADL, MMSE, FAQ, and CDR-SB; this will be performed using subjects from the LY3314814 dose groups and the placebo group. Correlation analyses will be conducted using only subjects who have the clinical outcome and plasma Aβ result at Week 71.

10.3.3.6.2. Analysis of vMRI Data

Analyses of the following vMRI parameters will be conducted:

- Right hippocampal volume (mm3)

- Left hippocampal volume (mm3)
- Right hippocampal volume (mm3) + Left hippocampal volume (mm3)
- Right entorhinal cortex (mm3)
- Left entorhinal cortex (mm3)
- Atrophy of Total whole brain volume (cm3)
- Enlargement of Ventricular volume (cm3)

To evaluate the changes in vMRI data after treatment, an analysis of covariance (ANCOVA) model will be used to compare change from baseline to 78 weeks. The change from baseline to the endpoint visit will be the dependent variable. The model for the fixed effects will include the independent effects baseline volumetric magnetic resonance imaging (vMRI) value and treatment. The null hypothesis is that the difference in LSM between the LY3314814 dose groups and placebo equal zero. A similar analysis will be performed for completers.

To assess the effects of various demographic and baseline characteristics, subgroup analyses of the change from baseline to 78 weeks in vMRI data will be performed. Two subgroups will be included for this analysis, provided there are at least 50 subjects for all categories of a subgroup in each treatment group: (1) ApoE4 carrier status (carrier [ε2/ε4, ε3/ε4, ε4/ε4], noncarrier [ε3/ε3, ε2/ε2, ε3/ε2]) and (2) ApoE4 genotype (ε2/ε4, ε3/ε4, ε4/ε4, no ε4). These analyses will be carried out using an ANCOVA model including the independent effects baseline vMRI value and treatment as well as the subgroup of interest and the subgroup-by-treatment interaction.

Annualized change in vMRI for each subject will be calculated using the change in vMRI at the last post-baseline visit. The annualized change will be compared between the treatment groups with an ANCOVA model. The ANCOVA model will include the independent variables baseline vMRI value and treatment. The null hypothesis is that the difference in LSM between the LY3314814 dose groups and placebo equal zero.

To assess the relationship of vMRI with cognition and function with treatment, Spearman's rank correlation coefficient will be obtained on change from baseline to Week 78 for vMRI parameters with change from baseline to Week 78 for ADAS-Cog_{13}, ADCS-iADL, MMSE, FAQ, and CDR-SB; this will be performed using all subjects who have the clinical outcome and vMRI result at Week 78.

10.3.3.6.3. Analysis of Amyloid PET Imaging

Florbetapir PET scans provide an in vivo measurement of deposited amyloid plaques in the brain. Florbetapir cortical composite SUVr correlates with post-mortem assessments of amyloid plaque load (Clark et al. 2012; Joshi et al. 2015). Florbetapir amyloid scans will be performed at screening, 78 and 156 weeks. The change in SUVr between baseline and follow-up scans will be compared across treatment groups and to total exposure to LY3314814.

Change in SUVr will be examined using an ANCOVA model containing terms for baseline SUVr, treatment, and age at baseline. The null hypothesis is that the difference in LSM between

the LY3314814 dose groups and placebo equals zero. Further details regarding the analysis will be provided in the SAP.

10.3.3.6.4. Analysis of Cerebrospinal Fluid

To evaluate the change in CSF biomarkers (including sAPPβ, total CSF $A\beta_{1-40}$, total CSF $A\beta_{1-42}$, CSF total tau, and CSF p-tau from lumbar puncture) after treatment, the same MMRM model used for analysis of plasma Aβ results will be used. The null hypothesis is that the difference in LSM between the LY3314814 dose groups versus placebo equal zero. Similar analyses will be performed for completers.

Annualized change in CSF biomarkers for each subject will be calculated using the change in CSF at the last post-baseline visit. The annualized change will be compared between the treatment groups with an ANCOVA. The ANCOVA model will include the independent variables baseline CSF value and treatment. The null hypothesis is that the difference in LSM between the LY3314814 dose groups and placebo equal zero.

To assess the relationship of CSF parameters with cognition and function with treatment, Spearman's rank correlation coefficient will be obtained on change in CSF result from baseline to Week 71 versus changes in, ADAS-Cog_{13}, ADCS-iADL, MMSE, FAQ, and CDR-SB; this will be performed using all subjects who have the clinical outcome and CSF result at Week 71.

Further details regarding the analysis will be provided in the SAP.

10.3.3.6.5. Analysis of Florbetapir Perfusion (rCBF)

An additional perfusion-weighted image may be acquired at each florbetapir PET scanning visit, with no additional tracer injection, by utilizing the initial wash-in of florbetapir to the brain (see Section 9.8.2.1). These images will provide a perfusion (or blood flow) map in the brain. In Alzheimer's disease, cerebral perfusion is reduced, especially in temporal and parietal areas, and this pattern of hypoperfusion closely mirrors the hypometabolism pattern observed using 18F-FDG PET (Hsiao et al. 2012). As such, the perfusion PET images provide a biomarker of brain function. Changes in florbetapir perfusion PET-based rCBF between the baseline and follow-up scans will be compared across treatment groups and to total exposure to LY3314814. Change in rCBF will be examined using an ANCOVA model with fixed effects of baseline biomarker result and treatment. The null hypothesis is that the difference in LSM between the LY3314814 dose groups and placebo equals zero.

To assess the relationship of rCBF with cognition and function with treatment, Spearman's rank correlation coefficient will be obtained on change from baseline to Week 78 and with change from baseline to Week 156 for, ADAS-Cog_{13}, ADCS-iADL, MMSE, FAQ, and CDR-SB. Correlation analyses will be conducted using only subjects who have the clinical outcome and rCBF result at Week 78 and include subjects from all three dose groups.

Further details regarding the analysis will be provided in the SAP.

10.3.3.7. Tertiary/Exploratory Analyses

Tertiary and exploratory analyses will be detailed in the SAP.

10.3.4. Safety Analyses

Safety will be assessed by summarizing and analyzing AEs, laboratory analytes, vital signs, MRI scans, skin and eye examinations, and ECGs during the treatment period.

Safety analyses for the Placebo-Controlled period will include comparisons between LY3314814 dose groups and placebo. All hypotheses will be tested at a 2-sided 0.05 significance level. No adjustments for multiple comparisons will be made.

Safety analyses for the Delayed-Start period will incorporate a "contextualizing cohort" developed through modeling the plausible progression of disease for a placebo treated cohort. Further details on this modeling approach and the analysis methods will be outlined in the SAP.

For analysis comparing proportion of treatment-emergent abnormalities between treatment groups for laboratory analytes, vital signs, weight, MRI scans, skin and eye examinations, and ECGs, only patients who have both a baseline observation and a postbaseline observation will be included in the analysis for each analyte or parameter, respectively.

Suicide-related thoughts and behaviors, based on the C-SSRS, will be listed by patient and visit. Only patients that show suicidal ideation/behavior will be displayed (that is, if a patient's answers are all "no" for the C-SSRS, then that patient will not be displayed). However, if a patient reported any ideation or behavior at any time point, then all their ideation and behavior will be displayed, even if not positive.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

The details of the PK/PD analysis plan will be described in a separate document. It is intended that the data from this study will be combined with data from other studies of LY3314814 in a meta-analysis, to characterize the PK/PD of LY3314814 and AZ13569724, and to investigate the effects of certain potential covariates on LY3314814 PK. The PK analysis will be conducted using Nonlinear Mixed Effects Modeling (NONMEM) software. To facilitate this modeling, and to ensure that exposure estimates from this study are available at the end of the Placebo-Controlled treatment period, it is intended that the PK data will be locked after all patients complete Visit 12 (52 weeks of treatment), to allow PK modeling to begin before the end of the Placebo-Controlled treatment period. No safety or efficacy data will be included in the 52-week PK lock. An Early PK Lock Plan will be developed and implemented prior to this lock, which will specify the safeguards to be taken to ensure the integrity of the study. It is intended that the results of the PK analysis will be provided in a separate report.

Cerebrospinal fluid LY3314814 and CSF Aβ concentrations will be summarized by doses, and mean change from baseline following drug treatment will be calculated. Additional analyses may be conducted, as warranted. The results of these analyses will be reported with the results of the plasma PK analysis.

The following analyses will be conducted using data from the Placebo-Controlled portion of the trial, after all patients have completed that portion of the trial:

1. It is intended that plasma Aβ concentrations will be summarized for each visit and doses. Other analyses may be conducted, as warranted. The results of these analyses will be reported with the results of the plasma PK analysis.
2. It is intended that the relationship between plasma exposure and change in clinical endpoints (including, but not limited to ADAS-Cog_{13} and ADCS-iADL score) will be evaluated graphically. Additional methods may be used to describe the exposure-response relationship. The results of these analyses will be reported with the results of the plasma PK analysis.

10.3.6. Other Analyses

10.3.6.1. Health Economics

Shifts from baseline in quality of life as measured by the proxy version of the EQ-5D and QoL-AD will be presented. Also, resource utilization as measured by RUD-Lite (basic ADL hours/day, instrumental ADL hours/day, supervision hours/day, and the sum of basic and instrumental ADL hours/day) will be presented. These analyses will compare treatment groups in the same manner as described for the primary efficacy analysis.

Number of hospitalizations will be compared across treatment groups using Fisher's Exact test. The proportion of subjects who have a change in permanent living accommodation will be summarized and treatment comparisons will be conducted using Fisher's Exact Test. Study partner change from previous visit (yes/no) will be summarized by treatment group. Incidence of study partner change will be compared across treatment groups using Fisher's Exact test.

10.3.6.2. Subgroup Analyses

To assess the effects of various demographic and baseline characteristics, subgroup analyses of the primary endpoint for the Placebo-Controlled period, ADAS-Cog_{13}, will be performed based on the following variables: gender, age, race, APOE4 carrier status, country, concomitant AD therapy, compliance with investigational product, and reason for discontinuation. The specific grouping of patients based on these variables will be outlined in the SAP. All subgroup analyses will be considered secondary analyses.

10.3.7. Interim Analyses

An interim futility analysis may be conducted by the IDMC, for example, if study AZES is stopped for futility. The purpose of this interim analysis is to potentially stop either dose or both doses early for futility.

Only the IDMC 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 their patients.

A limited number of pre-identified individuals may gain access to a limited set of unblinded data, as specified in the unblinding plan, prior to the final database lock, in order to initiate the final population PK model development processes for interim or final analyses. The details of this data set will be specified in a separate unblinding plan document, but will generally include PK

data, demographic data, and other information required to facilitate PK model development. This data set will not include safety or efficacy endpoints. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

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

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
Aβ	amyloid beta peptide
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
AD8	Eight-item Interview to Differentiate Aging and Dementia
ADAS-Cog$_{13}$	13-item Alzheimer's Disease Assessment Scale-Cognition
ADCS-ADL	Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ApoE4	apolipoprotein E4
APP	amyloid precursor protein
ARIA-E	amyloid-related imaging abnormality–edema/effusions (also known as vasogenic edema)
ARIA-H	amyloid-related imaging abnormality–hemosiderin deposition (also known as microhemorrhage)
AST	aspartate aminotransferase
AV	atrioventricular
AZ13569724	O-dealkylated metabolite of LY3314814 (also known as AZD3293)
BACE	Beta-site amyloid precursor protein cleaving enzyme
BCRP	breast cancer resistance protein

blinding	A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CDR/CDR-SB	Clinical Dementia Rating/ Clinical Dementia Rating–Sum of Boxes
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
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 the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
CRF	Case report form (sometimes referred to as clinical report form). A printed or electronic form for recording study patients' data during a clinical study, as required by the protocol.
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.
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CYP3A4	cytochrome P450 3A4
ECG	electrocardiogram
eCOA	Electronic Clinical Outcome Assessments
eCRF	electronic case report form (see CRF)
ED	Early discontinuation
efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result under controlled conditions.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D Proxy	EuroQol 5-Dimensional Health-Related Quality of Life Scale proxy version
FAQ	Functional Activities Questionnaire
FDA	Food and Drug Administration

FDG	Fluorodeoxyglucose
florbetapir	[18F]-AV-45 (chemical name (E)-4-(2-(6-(2-(2-(2-[18F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-Nmethylbenzenamine)
GCP	good clinical practice
GMP	Good Manufacturing Practice
HCV	Hepatitis C virus
HDL	High-density lipoproteins
HBsAg	Hepatitis B surface antigen
iADRS	integrated Alzheimer's Disease Rating Scale
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IgG/IgM	immunoglobulin G/immunoglobulin M
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient'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.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRB/ERB	Institutional Review Board/Ethical Review Board: a board or committee (institutional, regional, or national) composed of medical professional and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.

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 patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients 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.
IxRS	interactive voice-response system (IVRS) and interactive web-response system (IWRS)
LDL	Low-density lipoproteins
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.
Lilly	Eli Lilly and Company
LOCF	last observation carried forward
LP	lumbar puncture
LSM	Least squares means
MCI	Mild cognitive impairment
MMRM	mixed-model repeated-measures
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NIA-AA	National Institute on Aging (NIA) and the Alzheimer's Association (AA)
NPI	Neuropsychiatric Inventory
PCR	polymerase chain reaction
PET	positron emission tomography
Pgp	P-glycoprotein
PK/PD	pharmacokinetics/pharmacodynamics
QoL-AD	Quality of Life in Alzheimer's Disease (scale)
QTc	corrected QT interval
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBC	Red blood cells
rCBF	Regional cerebral blood flow
RNA	ribonucleic acid

RUD-Lite	Resource Utilization in Dementia-Lite
ULN	Upper limit of normal
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.
SUSARs	suspected unexpected serious adverse reactions
SUVr	standard uptake value ratio
TBL	total bilirubin level
TPO	third-party organizations
VAS	visual analog scale
vMRI	volumetric magnetic resonance imaging
WBC	White blood cells

Appendix 2. Clinical Laboratory Tests and Other Biomarkers

Variables in serum/blood and urine

Hematology (blood)
Hematocrit
Hemoglobin
Erythrocyte (RBC) count
Mean cell volume
Mean cell hemoglobin concentration
Leukocytes (WBC)
Neutrophils, segmented
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelet counts

Coagulation
Prothrombin time[a]
Partial thromboplastin time[a]
International normalized ratio (INR)[a]

Clinical chemistry (serum)
Alanine aminotransferase (ALT)
Albumin
Alkaline phosphatase
Aspartate aminotransferase (AST)
Bilirubin, fractionated[a]
Bilirubin, total[b]
Blood urea nitrogen (BUN)
Cholesterol (total, HDL, LDL) and triglycerides[e]
Calcium, total
C-reactive protein
Creatine kinase (CK)
Creatinine
Creatinine clearance[a]
Glucose

Endocrinology
Thyroid-stimulating hormone[e]
Total thyroxine[e]

Electrolytes (serum)
Bicarbonate
Chloride
Phosphate
Potassium
Sodium

Urinalysis
Blood
Color
Glucose
Ketones
Leukocyte esterase
pH
Protein
Specific gravity

Screening tests[a]
Folic acid
Hepatitis B surface antigen (HBsAg)[c]
Hepatitis C virus (HCV) PCR[d]
Vitamin B12

Other
Hemoglobin A1c (HbA1c)[e]

Optional
(tested at the discretion of the investigator or if mandated by local regulatory authority)
Human immunodeficiency virus[a]

Abbreviations: HDL = High-density lipoproteins; LDL = Low-density lipoproteins; PCR = polymerase chain reaction; RBC = red blood cells; WBC = white blood cells.

[a] At screening only.

[b] Done at all other times besides screening.

[c] At screening only in patients with suspected or past history of Hepatitis B.

[d] At screening only in patients with suspected or past history of Hepatitis C.

[e] At screening, Week 26, Week 52, and Week 78 (or final study visit) only for the Placebo-Controlled period as well as Week 104, Week 130, and Week 156 (or final study visit) only for the Delayed-Start period.

Note: Laboratory values outside the reference limit suspected to be of any clinical significance will be repeated. Patients for whom suspected clinical significance is confirmed will either not be enrolled or, if already enrolled, will be followed until normalization or for as long as the Investigator considers necessary. Additional laboratory tests may be performed for safety reasons if judged appropriate by the investigator. See Section 9.4.4 for information regarding the recording of AEs based on laboratory tests. All laboratory samples will be analyzed using routine methods per the central laboratory, as referenced in the Laboratory Manual for this study.

For blood volume, see Appendix 5.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for ensuring:

- that the patient and study partner understands the potential risks and benefits of participating in the study
- that informed consent is given by each patient or legal representative and their study partner. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient and study partner may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.
- As used in this protocol, the term "informed consent" includes all consent and assent given by patient or their legal representatives and by study partner.

Appendix 3.1.2. Ethical Review

The investigator or an appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Conference on Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to the Sponsor before the study may begin at the investigative site(s). The Sponsor or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study site's ERB(s) should be provided with the following:

- the current Investigator Brochure (IB) and updates during the course of the study
- informed consent and Assent Form
- relevant curricula vitae

Appendix 3.1.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party.

Appendix 3.1.4. Investigator Information

Physicians with expertise in neurology, geriatrics, or psychiatry who have clearly documented extensive experience in AD trials will participate as investigators in this clinical study. In addition, licensed clinicians who have clearly documented experience in AD trials may participate as investigators in this clinical study upon approval by the Sponsor.

Appendix 3.1.5. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Sponsor representative or designee.

Appendix 3.1.6. Final Report Signature

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax

- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, the Sponsor or its representatives will periodically check a sample of the patient and study partner data recorded against source documents at the study site. The study may be audited by the Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Electronic Clinical Outcome Assessments- (eCOA) measures (for example, a rating scale) are entered into an eCOA instrument at the time that the information is obtained. In these instances where there is no prior written or electronic source data at the site, the eCOA instrument record will serve as the source.

Electronic Clinical Outcome Assessments records are stored at a third party site, and investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the eCOA instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Sponsor data warehouse.

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if the Sponsor or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

The study will be discontinued if the Sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Sponsor-designated medical monitor.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Cytomegalovirus antibody, IgG and IgM
	Epstein-Barr virus VCA antibody, IgG and IgM[c]
	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis C RNA PCR
Direct bilirubin	Hepatitis E antibody, IgG and IgM
Alkaline phosphatase	
ALT	
AST	**Anti-nuclear antibody[a]**
GGT	
CPK	**Alkaline Phosphatase Isoenzymes[a]**
PK for LY3314814	**Anti-smooth muscle antibody (or anti-actin antibody)[a]**
	Type I anti-liver kidney microsomal antibodies

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; IgG/IgM = immunoglobulin G/immunoglobulin M; INR = international normalized ratio; PCR = polymerase chain reaction; RBC = red blood cells; RNA = ribonucleic acid; WBC = white blood cells; VCA = viral capsid antigen.

[a] Assayed by Sponsor-designated or local laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

[c] If EBV VCA antibody unavailable, obtain heterophile antibody of monospot testing

Appendix 5. Sampling Summary

This table summarizes the approximate number of samples venipunctures and lumbar puncture and volumes for all sampling screening, standard laboratory, drug concentration, pharmacogenetic, biomarker, and exploratory and tests during the study. Fewer samples may actually be taken, but this will not require a protocol amendment.

Protocol I8D-MC-AZET Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Screening tests[a]	Blood	3.5 mL	6	16 mL
Standard laboratory tests[a]	Blood	2.5 mL	40	92 mL
Lumbar puncture	CSF	18 mL	3	54 mL
Drug concentration	Blood	3 mL	13	39 mL
Pharmacogenetic samples	Blood	6 mL	1	6 mL
Other exploratory samples	Blood	10 mL	31	133 mL
Total Blood and CSF				340 mL
Hepatic Monitoring[b]	Blood	3 - 30 mL	-	-

Abbreviation: CSF = cerebrospinal fluid; mL = milliliter

[a] Additional samples may be drawn if needed for safety purposes.

[b] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with Sponsor-designated Medical Monitor.

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