Protocol I8D-MC-AZFD(a)

A Randomized, Double-Blind, Delayed-Start Study of LY3314814 (AZD3293) in Early Alzheimer's Disease Dementia (Extension of Study AZES, The AMARANTH Study)

NCT02972658

Approval Date: 06-Feb-2018

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A Randomized, Double-Blind, Delayed-Start Study of LY3314814 (AZD3293) in Early Alzheimer's Disease Dementia (Extension of Study AZES, The AMARANTH Study)

LY3314814 (Lanabecestat)

Study AZFD is a Phase 3 study designed to test whether LY3314814 will slow disease progression in patients with early Alzheimer's Disease randomized in Study AZES.

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

Approval Date: 06-Feb-2018 GMT

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1. Synopsis

Title of Study:

A Randomized, Double-Blind, Delayed-Start Study of LY3314814 in Early Alzheimer's Disease Dementia (extension of Study AZES).

Rationale:

LY3314814 is being developed for the modification of the clinical course of Alzheimer's disease (AD) by slowing disease progression in patients diagnosed with early AD, which is defined as the continuum of patients with mild cognitive impairment due to AD (MCI-AD) and patients diagnosed with mild AD dementia. Study AZFD integrated with Study AZES forms a Delayed Start study (Study AZES-FD). Study AZES-FD will be used to test the hypothesis that patients originally randomized to receive placebo in the double-blind feeder Study AZES and switched to LY3314814 at the start of Study AZFD do not "catch up" on the Alzheimer's Disease Assessment Scale-Cognitive Subscale ($ADAS\text{-}Cog_{13}$) at Week 26 (Visit 7) of Study AZFD to patients originally randomized to receive LY3314814 in the double-blind feeder study.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • The primary analysis of Study AZES-FD is to evaluate disease modification as outlined in Liu-Seifert (2015). This will be accomplished by testing the three delayed-start hypotheses in both doses of LY3314814 across Study AZES and up to Week 26 (Visit 7) of Study AZFD.	• $ADAS\text{-}Cog_{13}$
Secondary *Clinical efficacy objective:* • To evaluate the disease modification of both doses of LY3314814 on functional and cognitive outcomes across Study AZES and up to Week 26 (Visit 7) of Study AZFD using the primary analysis methodology.	• Functional Outcome Measures o ADCS-ADL score o FAQ • Cognitive/Functional Outcome Measures o iADRS score o CDR-SB • Cognitive Outcome Measures o MMSE
• The delayed-start analyses as outlined above will also be examined through Week 104 (Visit 15) for cognitive and functional outcomes.	• $ADAS\text{-}Cog_{13}$, ADCS-ADL, FAQ, iADRS, CDR-SB, MMSE
Safety Objective • Collect information in order to further characterize the safety and tolerability of LY3314814 in patients with early AD	• Standard safety assessments: o spontaneously reported AEs o clinical laboratory tests o vital sign and body weight

Objectives	Endpoints
dementia (at the time of entry into Study AZES)	measurements o 12-lead ECGs o physical examinations including neurological examinations • Additional safety assessments: o Eye examinations o Skin examinations o Serial MRI o Columbia-Suicide Severity Rating Scale (C-SSRS)

Abbreviations: AD = Alzheimer's disease; ADAS-Cog_{13} = 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; AE = adverse event; CDR-SB = Clinical Dementia Rating Sum of Boxes; ECG = electrocardiogram; FAQ = Functional Activities Questionnaire; iADRS = integrated Alzheimer's Disease Rating Scale; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging.

Summary of Study Design:

Study I8D-MC-AZFD is a multicenter, randomized, double-blind, 104-week delayed-start study with 2 fixed doses of LY3314814 in patients diagnosed with early AD, which is defined as the continuum of patients with MCI-AD and patients diagnosed with mild dementia of the Alzheimer's type (mild AD dementia), at the time of entry into feeder Study AZES.

Treatment Arms and Duration:

In Study AZFD, all patients will receive treatment with LY3314814. Patients who were randomized to LY3314814 in feeder Study AZES will continue with the same drug dose in Study AZFD. Patients who were randomized to placebo in the feeder study will be randomized, in a 1:1 ratio, to either LY3314814 20 mg or LY3314814 50 mg. All patients will receive study drug for 104 weeks.

Number of Patients:

It is estimated that approximately 1540 patients will complete the feeder Study AZES. Of those patients who complete Study AZES, it is assumed that approximately 90% (1400) of the patients will provide consent to continue into Study AZFD.

Statistical Analysis:

The statistical analyses outlined in this protocol pertain to the delayed-start Study AZES-FD. Because Study AZFD forms the second part of a delayed-start study design when paired with Study AZES, safety and efficacy analyses of Study AZFD alone are difficult to interpret and are not planned a priori.

2. Schedule of Activities

Study procedure[a]	Delayed-Start Year 1											Delayed-Start Year 2				ED[b]	F/U
Visit number	**V20-AZES/ V1-AZFD[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8[d]**	**V9**	**V10**	**V11**	**V12[e]**	**V13**	**V14**	**V15**		**V801[f]**
Study week		**1**	**4**	**7**	**13**	**19**	**26**	**32**	**39**	**45**	**52**	**65**	**78**	**91**	**104**		
Tolerance interval for Visit (days)		**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±10**	**±7**	**±7**	**±7**	**±7**		
Informed consent	X																
Randomization	X																
Prior/concomitant treatments	CO	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X																
NIA-AA criteria review										X				X		X	
FAQ	CO						X				X		X		X	X	
ADCS-ADL	CO						X				X		X		X	X	
CDR[g]	CO						X				X		X		X	X	
MMSE	CO				X		X				X		X		X	X	
RBANS										X				X		X	
ADAS-Cog_{13}	CO				X		X				X		X		X	X	
NPI	CO						X				X		X		X	X	
Letter & Category Fluency, Digit Symbol-Coding tests	CO						X				X		X		X	X	
EQ-5D-5L (patient)	CO					X				X					X	X	
RUD-Lite	CO					X				X					X	X	
MRI	CO										X				X	X	
Florbetapir F18 Amyloid PET[h]	CO										X					X[i]	
Required blood samples for plasma biomarkers[j]							X[j]				X[j]					X[i,j]	
Laboratory tests[k]	CO		X	X	X		X		X		X	X	X	X	X	X	
Physical, neurological examinations	CO		X[l]		X		X[l]		X[l]		X	X[l]	X	X[l]	X	X	
Comprehensive eye examination	CO										X				X	X	
Skin examination	CO				X						X				X	X	
Vital signs[m]	CO	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Body weight	CO				X		X				X				X	X	

Study procedure[a]	Delayed-Start Year 1											Delayed-Start Year 2				ED[b]	F/U
Visit number	**V20-AZES/ V1-AZFD[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8[d]**	**V9**	**V10**	**V11**	**V12[e]**	**V13**	**V14**	**V15**		**V801[f]**
Study week		**1**	**4**	**7**	**13**	**19**	**26**	**32**	**39**	**45**	**52**	**65**	**78**	**91**	**104**		
Tolerance interval for Visit (days)		**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±10**	**±7**	**±7**	**±7**	**±7**		
12-lead ECG[n]	CO	X	X		X		X		X		X		X		X	X	X
C-SSRS and Self-Harm Supplement Form[o]	CO	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Dispense drug	X	X	X	X	X	X	X		X	X	X	X	X	X			
Assess drug compliances[p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	CO	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FDG PET[q]	CO										X					X[r,i]	
or Flortaucipir F 18 PET[q]	CO										X					X[r,i]	
Consent for optional DNA/RNA blood sample[s]	X																
Blood sample for DNA[t] (optional)							X									X[u]	
Blood sample for RNA[t] (optional)							X				X					X[i]	

Abbreviations: ADAS-Cog$_{13}$ = 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL = the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; Aβ = A-beta amyloid; CDR = Clinical Dementia Rating; CO = Carryover; C-SSRS = Columbia Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ED = early discontinuation; EQ-5D-5L (patient) = 5-dimensional EuroQol quality of life scale; FAQ = Functional Activities Questionnaire; FDG = fludeoxyglucose; F/U = follow-up; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NIA-AA = National Institute of Aging – Alzheimer's Association; NPI = Neuropsychiatric Inventory; PET = positron emission tomography; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RNA = ribonucleic acid; RUD-Lite = Resource Utilization in Dementia – Lite; V = visit.

[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 (i.e., visits should be scheduled based on the randomization date rather than the previous visit). Even if a patient enters into Study AZFD, it is expected that the patient complete all Study AZES procedures. Any missing procedures should be completed during the maximum time window of the Study AZES follow-up period (6 weeks). Studies AZES and AZFD are considered compatible studies.

[b] All patients who discontinue study treatment before Visit 15 should have Early Discontinuation (ED) procedures and assessments performed as soon as possible. ADCS-ADL, FAQ, CDR, MMSE, RBANS, ADAS-Cog$_{13}$, NPI, and Letter & Category Fluency, Digit Symbol-Coding tests should be conducted at the early discontinuation visit if it has been more than 12 weeks since they were last administered. If it has been >6 months since the last MRI, then an MRI is performed. PET scans (applicable to a subset of patients) should be performed if discontinuation occurs between Visit 6 and Visit 11.

[c] First dose to be administered the day after completion of Visit 1, preferably in the morning.

[d] Visit 8 is conducted by telephone and may include either the patient or the study partner, or both, as appropriate. The patient or study partner may be required to visit the clinic if drug dispensing is needed.

[e] The initiation of Visit 12 may be delayed for the patients who have completed the first year of the protocol prior to regulatory and ethics approval of the protocol amendment that includes the Year 2 extension.

[f] Patients who complete study treatment or have early discontinuation should participate in a follow-up visit (Visit 801), 4 to 6 weeks after the last dose of study treatment.

[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 approximately the same time of day at designated study visits, if possible.

[h] Assessment performed only for those patients who had florbetapir F 18 PET scan at Visit 20 in Study AZES. Patients with current participation in a research and/or medical protocol involving PET ligands or radioactive agents judged not to be scientifically or medically compatible with this study, with exposure to ionizing radiation that in combination with the planned administration of study florbetapir PET ligand would result in a cumulative exposure that exceeds local recommended exposure limits, or hypersensitivity to the active substance or any of the excipients of florbetapir F 18 are excluded from obtaining the florbetapir PET scan.

[i] If discontinuation occurs after Visit 11, it is not collected or performed.

[j] Blood samples for determination of plasma biomarkers ($A\beta_{1-40}$, $A\beta_{1-42}$) will preferably be collected 2 to 3 hours post-dose at indicated visits and failure to collect within this time frame will not be considered a protocol deviation. Blood samples for other exploratory plasma biomarkers will also be collected at indicated visits.

[k] Hematology, clinical chemistry, electrolytes, and urinalysis are included in every laboratory determination. Thyroid-stimulating hormone, total thyroxine and hemoglobin A1c will be measured at Visits 11, and 15 or ED.

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

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

[n] Single safety ECGs are required.

[o] The Adult C-SSRS Since Last Visit version will be 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 (SHFU) form will be used to collect additional information to allow for a more complete assessment of these behaviors.

[p] 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. During visits conducted by telephone, the patient or study partner will be questioned about compliance with study treatment.

[q] Patients who participated in Study AZES FDG PET or flortaucipir F 18 PET addenda will have the option to continue in the addendum to which they were previously assigned, provided that they consent for these procedures in Study AZFD.

[r] If the patient discontinues study treatment between Visit 6 and Visit 11, the FDG or flortaucipir F 18 addendum PET scan should be performed.

[s] Participation in this procedure is optional and consent can occur any time before blood draw.

[t] Patients who participate in optional pharmacogenomics samplings will be provided a separate informed consent for the samplings. Failure to participate in optional sampling will have no influence on the eligibility of the patient for the study. Consent can be obtained any time before blood draw.

[u] Blood sample should be collected at ED visit if the patient discontinues prior to Visit 7.

3. Introduction

3.1. Study Rationale

Eli Lilly and Company (Lilly) and AstraZeneca (AZ) have entered into an alliance to develop LY3314814 (AZD3293). Throughout this document, only the Lilly compound identifier (LY3314814) will be used since Lilly is designated as the sponsor. In addition, the Study code I8D-MC-AZFD/D5010C00030 will be referred to as Study I8D-MC-AZFD or Study AZFD throughout this document.

LY3314814 is being developed for the modification of the clinical course of Alzheimer's disease (AD) by slowing disease progression in patients diagnosed with early AD, which is defined as the continuum of patients with mild cognitive impairment due to AD (MCI-AD) and patients diagnosed with mild dementia of the Alzheimer's type (mild AD dementia) randomized to Study AZES. Study I8D-MC-AZFD will test the hypothesis that patients originally randomized to receive placebo in the double-blind feeder Study AZES and switched to LY3314814 at the start of Study AZFD do not "catch up" on the Alzheimer's Disease Assessment Scale-Cognitive Subscale ($ADAS\text{-}Cog_{13}$) at Week 26 (Visit 7) of Study AZFD to patients originally randomized to receive LY3314814 in the double-blind feeder Study AZES. Additionally, secondary delayed-start analyses will also be conducted over the entire 104 weeks of treatment. Data acquired will also be used to evaluate the long-term safety and efficacy profile of LY3314814.

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 $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ in mice, rats, guinea

pigs, dogs, and humans. At sufficient exposures, LY3314814 reduces Aβ levels in the brain and cerebrospinal fluid (CSF).

Study AZFD is the third Phase 3 study in the LY3314814 registration program. For the purposes of this protocol, patients are considered eligible on the basis of early AD at the time of their enrollment into Study AZES, regardless of progression during their study participation.

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 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

Objectives	Endpoints
Primary • The primary analysis of Study AZES-FD is to evaluate disease modification as outlined in Liu-Seifert (2015). This will be accomplished by testing the three delayed-start hypotheses in both doses of LY3314814 across Study AZES and up to Week 26 (Visit 7) of Study AZFD.	• ADAS-Cog$_{13}$
Secondary *Clinical efficacy objective:* • To evaluate the disease modification of both doses of LY3314814 on functional and cognitive outcomes across Study AZES and up to Week 26 (Visit 7) of Study AZFD using the primary analysis methodology.	• Functional Outcome Measures o ADCS-ADL score o FAQ • Cognitive/Functional Outcome Measures o iADRS score o CDR-SB • Cognitive Outcome Measures o MMSE
• The delayed-start analyses as outlined above will also be examined through Week 104 (Visit 15) for cognitive and functional outcomes.	• ADAS-Cog$_{13}$, ADCS-ADL, FAQ, iADRS, CDR-SB, MMSE
Safety Objective • Collect information in order to further characterize the safety and tolerability of LY3314814 in patients with early AD dementia (at the time of entry into Study AZES)	• 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 Columbia-Suicide Severity Rating Scale (C-SSRS)

Abbreviations: AD = Alzheimer's disease; ADAS-Cog$_{13}$ = 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; AE = adverse event; CDR-SB = Clinical Dementia Rating Sum of Boxes; ECG = electrocardiogram; FAQ = Functional Activities Questionnaire; iADRS = integrated Alzheimer's Disease Rating Scale; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging.

5. Study Design

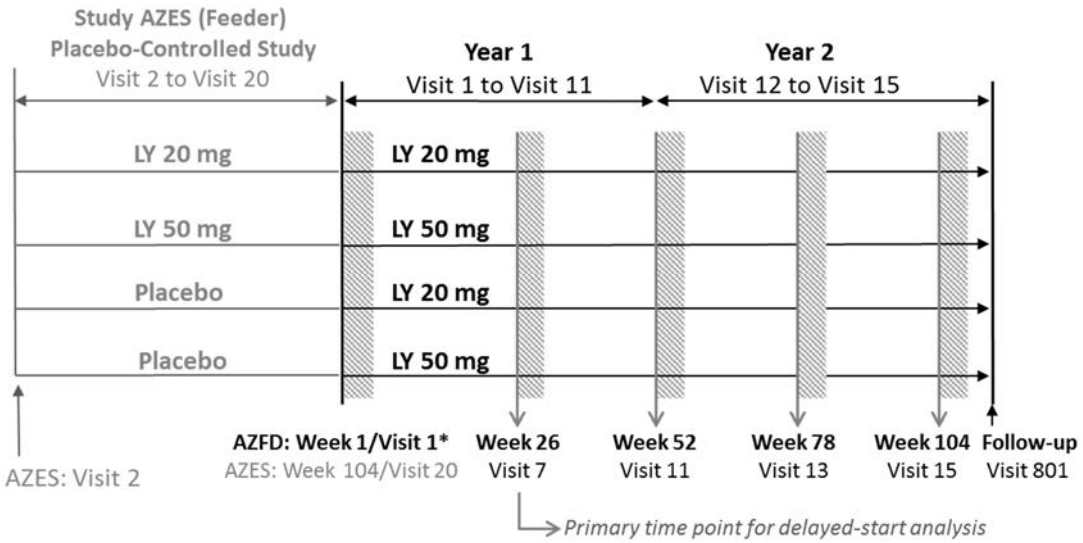
5.1. Overall Design

Study AZFD is a multicenter, randomized, parallel-group, double-blind, 104-week-long study of 2 fixed dose levels of LY3314814 in patients with early AD at the time of enrollment into the feeder Study AZES. The actual number of patients to be enrolled is dependent on the number of eligible patients completing feeder Study AZES.

The treatment period of this delayed-start extension will begin at the conclusion of Visit 20 of the feeder Study AZES which will also serve as Visit 1 for Study AZFD, and will continue with 104 weeks of treatment. Patients who were randomized in Study AZES to either 20 mg or 50 mg of LY3314814 will continue on the treatment allocation from the feeder study. Patients randomized to placebo in Study AZES will be randomized in a blinded fashion 1:1 to LY3314814 20 mg or 50 mg daily (QD), administered orally. Neither the patient nor investigator will be unblinded to feeder study treatment assignments. Assessments will be made as indicated on the Study Schedule of Activities found in Section 2.

The study includes a longitudinal florbetapir F 18 amyloid positron emission tomography (PET) scan for those patients who had a florbetapir F 18 PET scan at Visit 20 of Study AZES. In addition, there are two longitudinal addenda of fluorodeoxyglucose (FDG) PET and ^{18}F-AV-1451 PET at applicable sites. Patients who participated in these addenda in Study AZES are eligible to participate in the respective addenda in Study AZFD. Figure 5.1 illustrates the study design.

The initiation of Visit 12 may be delayed for the patients who have completed the first year of the protocol prior to regulatory and ethics approval of the protocol amendment that includes the Year 2 extension.



Abbreviation: LY = LY3314814.

* At Visit 1 of Study AZFD (Visit 20 of Study AZES), patients randomized to placebo from Study AZES will be randomized 1:1 to LY 20 mg or LY 50 mg in Study AZFD.

Note: Gray boxes after Study AZFD Visits 1, 7, 11, 13, and 15 indicate the 4-week symptomatic treatment initiation window for subjects with progression of symptoms.

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

5.2. Number of Participants

It is estimated that approximately 1540 participants will complete the feeder Study AZES. Based on historical data, it is assumed that 90% (approximately 1400) of the participants from Study AZES will provide consent to continue participation in Study AZFD. Consent for Study AZFD may be obtained at any time prior to performing procedures specific only for Study AZFD.

5.3. End of Study Definition

The end of the study is defined as "the last visit of the last patient undergoing the study." This definition applies to the entire study and is not region specific.

The study is expected to start in Q1 of 2017 which is the scheduled date for the first completers of the feeder Study AZES. The final study visit will occur approximately 110 weeks after the last patient completes the feeder study.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if enrollment is slow. 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.

5.4. Scientific Rationale for Study Design

Study AZFD integrated with Study AZES forms a Delayed Start study design. Data from randomization (Visit 2) in Study AZES through Visit 7 of Study AZFD will be used to test whether there is a treatment effect that cannot be achieved with a later start of treatment. The time points beyond the primary analysis at 26 weeks (Visit 7) in Study AZFD will be analyzed upon last patient visit to determine the robustness of early treatment over the full 104-week delayed-start 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 generally safe and well tolerated in the Phase 1 studies and ongoing Phase 3 studies [I8D-MC-AZES, I8D-MC-AZET]. 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 generally safe and well tolerated.

6. Study Population

Eligible patients will be men and women completing feeder Study AZES. Eligible patients must have been randomized into Study AZES, and completed the primary protocol through Visit 20 without permanent discontinuation of study treatment.

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

6.1. Inclusion Criteria

General Inclusion Criteria

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

[2] Patients participating through Visit 20 of Study AZES and who have not permanently discontinued study treatment. Note: Patients who have permanently discontinued study treatment prior to Visit 20 of Study AZES and have remained in Study AZES off treatment are not eligible for Study AZFD.

[3] 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 as for Study AZES should participate, and this study partner should be willing to participate throughout this study and must have sufficient patient interactions to be able to provide meaningful input into the rating scales administered in this study, where study partner input is required, in particular for the CDR. 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. Evidence for adequacy of the study partner should be documented in source documentation. The study partner must be cognitively able to fulfill the requirements of the study, in the opinion of the investigator. 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).

[4] In the opinion of the investigator, the patient and study partner will be compliant with, and have a high probability of completing the study.

[5] Patients who are willing to complete the diagnostic and procedural assessments as defined in the protocol.

6.2. Exclusion Criteria

General Exclusion Criteria

[6] Patients should not have participated or currently participate in any other clinical trial or any other type of medical research judged not to be scientifically or medically compatible with this study for the duration of their participation in the current study.

[7] Meets discontinuation criteria of feeder Study AZES at the final visit of that study.

[8] Contradictions to continuing or starting therapy as per Study AZES protocol (that is, use of strong inhibitors/inducers of cytochrome P450 3A4 (CYP3A4), or use of strong inhibitors or inducers of P-glycoprotein (Pgp), or inhibitors of breast cancer resistance protein [BCRP]).

[9] 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.

[10] Current clinically important abnormality, as determined by the 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.

6.3. Lifestyle Restrictions

Patients will be required to:

1. Refrain from donating blood from the Visit 1 until 3 months after the follow-up visit.
2. Follow restrictions regarding concomitant medications according to Section 7.7.
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 sun protection factor of at least 15; and protect the lips with a lip balm containing sun block.
5. Men must abstain or be willing to use barrier contraception (i.e., condoms) and not donate sperm during the study participation, through 3 months after study participation ends. Men must also agree to abstain for 24 hours after PET scans.
6. Avoid excessive use of alcohol during study participation. 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) may not be rescreened.

6.5. Study Partner

Every patient in the study must have a study partner, who must sign an informed consent form (ICF). An identification number will be assigned to each study partner and recorded for each efficacy measure that the study partner provides input. 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 magnetic resonance imaging (MRI), PET or skin or eye examinations. The study partner should either co-habit with or have regular contact with the enrolled patient. While every effort should be made to maintain the same study partner for a given patient throughout the study, and if at all possible, the same study partner who participated in Study AZES, 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 and must sign an ICF and be assigned a new identification number. Demographic data, including year of birth, sex, and relationship to the patient, will be collected for every study partner.

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 AZ.

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 (see Table 7.1).

Patients who were on placebo in the feeder Study AZES will be randomized to either LY3314814 20 mg or LY3314814 50 mg; blinding is maintained to prior allocation and dose (see Table 7.1). Patients who were randomized to active study drug in the feeder study will continue on the same study drug dose.

Table 7.1. Treatment Regimens

Regimen	AZES Dose	AZFD Dose
Group 1	20 mg tablet	20 mg tablet Placebo to Match 50-mg tablet
Group 2	50 mg tablet	50 mg tablet Placebo to Match 20-mg tablet
Group 3	Placebo	20 mg tablet Placebo to Match 50-mg tablet
Group 4	Placebo	50 mg tablet Placebo to Match 20-mg tablet

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 Labeling

All study medication will be provided in child resistant blister packs. The blister packs will be further packaged 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.

Subjects randomized to the 20 mg dose group will receive a blister pack containing LY3314814 20 mg tablets and placebo tablets matching LY3314814 50 mg. Subjects randomized to the 50-mg dose group will receive a blister pack containing LY3314814 50 mg tablets and placebo tablets matching LY3314814 20 mg. All subjects will need to take two tablets daily (one of each size) in a double dummy fashion in order to the guarantee blinding.

All kits will bear a label 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 labeling.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized as the last procedure of Visit 1 of Study AZFD (Visit 20 of Study AZES). 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 kit containing double-blind investigational product to each patient. Site personnel will confirm that they have located the correct kit by entering a confirmation number found on the kits into the IxRS. Specific information concerning the use of the IxRS will be provided to the investigators.

To achieve between-group comparability for disease severity, the randomization will be stratified by disease severity at the time of randomization into Study AZES.

7.2.1. Selection and Timing of Doses

Patients will continue on Study AZES study treatment during the entire period of Visit 20 of Study AZES. To ensure that patients continue on study treatment without a lapse in therapy, patients will take their last dose of Study AZES treatment on the day of randomization into Study AZFD. Since many of the procedures and assessments will be used for both study visits, Visit 20 of Study AZES will occur simultaneously with Visit 1 of Study AZFD. Once all other AZES Visit 20 assessments and procedures have been completed, the final procedure in Study AZES is to assess drug compliance and collect any unused AZES study medication. After resolving Study AZES drug compliance, the patient can be randomized to the Study AZFD treatment. Patients are to take the first dose of Study AZFD treatment on the day following randomization into the study. The dose is to be taken once daily, preferably in the morning unless instructed otherwise.

Note: Every attempt should be made to ensure that the transition from Study AZES to Study AZFD is seamless. Any gaps in treatment should be minimized. If a gap in treatment occurs, please notify your Clinical Research Associate for Study AZFD.

7.3. Blinding

This is a double-blind study. Both patients and site personnel will remain blind to dose throughout the study.

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 prior to database lock for primary outcome, 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 Sponsor designated medical monitor.

7.7. Concomitant Therapy

Concomitant medications with the potential to affect cognition are permitted. These include, but are not limited to, cholinesterase inhibitors, opiates, ginkgo biloba and other approved nootropics, anxiolytics, antidepressants, sedative-hypnotics, hormone replacement therapy, sleeping aids, sedating anti-allergy medications, thyroid supplements, and vitamin E and vitamin B12 supplements (by injection). Maintaining consistency in testing conditions should be emphasized with respect to taking as-needed medications.

Patients may receive premedication for the MRI or PET assessments, but this medication should not be administered within 24 hours of any efficacy assessments.

After randomization, initiation, discontinuation, or dose adjustment of any therapy appropriate to the patient's condition is permitted, with the exception of those listed as prohibited. The Sponsor-designated medical monitor should be consulted as needed. Concomitant medications taken during the study must be recorded on the electronic case report form (eCRF), along with the indication, daily dose, and start and stop dates of administration. All patients will be questioned about concomitant medications at every study visit.

7.7.1. Initiation of Post-Randomization Symptomatic AD Treatments

Over the period of this trial patients may have progression of symptoms/disease (patients may progress to mild or moderate/severe stages of disease). For patients for whom treatment becomes medically indicated during the trial, initiation of cholinesterase inhibitors and memantine (moderate stages) is permitted. This initiation must only occur when medically indicated and documenting the rationale or indication for initiation will be required. In order to adequately capture any decline as well as stable improvements, these symptomatic treatments should be initiated within approximately four weeks after the completion of cognitive testing at the Visit 1, Visit 7, Visit 11, Visit 13, and Visit 15 (see Figure 5.1). Initiation at a time outside of these windows is discouraged, but the Sponsor-designated medical monitor should be contacted if a clinical need arises outside of the protocol-specified windows and will not be deemed a protocol violation if approved.

7.7.2. Other Medication Considerations Post-Randomization

Permitted concomitant medications should be maintained on a stable dose regimen during the study whenever possible. Attempts should be made to maintain stable doses of symptomatic AD medication, however, changes or additions are permitted when clinically indicated and must be documented in the eCRF.

As there is a potential for LY3314814 to influence digoxin levels due to effects of Pgp, it is recommended that digoxin levels be monitored when initiating and discontinuing test drug to avoid possible over- or under-digitalization. Other Pgp sensitive medications with very narrow therapeutic margins may also require monitoring or use with caution.

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

The following are prohibited concomitant medications during the study:

- Use of any investigational drug or device not specified in this study judged to be scientifically or medically incompatible with 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 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)

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 the Follow-up Visit (Visit 801).

7.8.2. Continued Access

Continued access would only be provided through a regulatory and IRB-approved protocol, where applicable. Safety and efficacy 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)
- ALT or AST >5X ULN for more than 2 weeks
- ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or prothrombin time >1.5X ULN
- ALT 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 elevations (ALP), if deemed of liver origin and drug-related as follows:
  - ALP >3X ULN
  - ALP >2.5X ULN and TBL >2X ULN
  - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Patients/subjects who discontinue treatment due to a hepatic event or abnormality of liver tests should have further clinical and laboratory monitoring and should have additional data collected using the hepatic safety eCRFs (HSCRF). The process should be initiated by the investigator in consultation with the sponsor-designated medical monitor.

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 cannot be met (see Section7.7.2).

- 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.

The study may be paused or stopped for safety by the Sponsor at any time.

Patients who discontinue the investigational product early will have early discontinuation (ED) procedures and follow-up visit performed as shown in the Schedule of Activities (Section 2). The follow-up visit should be performed within 4 to 6 weeks of discontinuing treatment.

8.1.2. Temporary Discontinuation from Study Treatment

Treatment suspension and re-dosing of study drug can be considered based on the Principal Investigator's judgment (examples include short-term treatment using a prohibited drug, uncertain adverse event, hospitalization). The maximum cumulative permissible treatment suspension during the course of Study AZFD is 3 weeks per study year over the duration of the study. Temporary treatment discontinuation and restarting needs to be documented. If temporary discontinuation is due to an AE, it should be reported to the Sponsor-designated medical monitor.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the Sponsor or investigator identifies 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 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 (for any reason, including early study termination as determined by the Sponsor and/or IDMC) will have ED 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.

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

Secondary efficacy variables in this study are the changes from baseline in Study AZES to Week 26 (Visit 7) in Study AZFD in FAQ score, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL), integrated Alzheimer's Disease Rating Scale (iADRS), CDR-SB, and Mini-Mental State Examination (MMSE).

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.

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 19, and the maximum instrumental items score (sum of individual instrumental item scores) is 59 (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.

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 to 144; with higher scores indicating greater impairment.

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.

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.

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).

Administration of the CDR 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

Letter Fluency, Category Fluency, and Digit Symbol-Coding tests. The Letter Fluency test is a measure of phonemic verbal fluency and executive functioning. The test consists of 3 trials. For each trial, the patient is asked to name as many words that start with a specific letter as he/she can in 60 seconds. Each trial is scored for the number of words correctly generated and number of errors. The total number of correct words and total errors are derived by summing the scores across the 3 trials.

The Category Fluency test is a measure of semantic verbal fluency and executive functioning. The patient is asked to name as many animals as he/she can in 60 seconds. The test yields scores for the number of correct animal names generated and the number of errors.

The Digit Symbol-Coding test from the Wechsler Adult Intelligence Scale-III (Wechsler 1997) engages multiple cognitive abilities, including attention, psychomotor speed, complex scanning, visual tracking, and immediate memory. The test instrument is composed of 140 small blank squares presented in 7 rows. Each blank square is randomly paired with a number (1 to 9) printed directly above it. A key printed above the rows of blank squares pairs each number with an unfamiliar symbol. After completing 7 practice items, the patient must use the key to fill in the blank squares in order (working left to right across the rows) with the symbol that is paired

with the number above it, working as quickly as possible within the time limit of 90 seconds. The test score is the number of blank squares filled in correctly within the time limit.

The Letter Fluency, Category Fluency, and Digit Symbol-Coding assessment results will be recorded on worksheets. Item-level scores from the worksheets will be transcribed into the eCRF.

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-5L (patient) provides a single index value for health status and is relevant to a wide range of health conditions and treatments. It is administered to the patient in only a few minutes and consists of 2 pages: the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (EQ VAS). The descriptive system covers 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each rated on 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

The EQ VAS records the patient's estimation of his/her health on a visual analogue scale with endpoints labeled "the best health you can imagine" and "the worst health you can imagine." This information can be used as a quantitative measure of patient health. The EQ-5D-5L asks the patient to mark an "X" on the scale to indicate his/her current health status.

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.

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.

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 dementia (Aronson et al. 2009; Orgogozo et al. 2004; Salloway 2004).

9.1.5. Order of Efficacy Assessments and Rater Qualifications

9.1.5.1. Order of Efficacy Assessments

Assessments administered to the patient are the MMSE; RBANS; ADAS-Cog_{13}; Letter Fluency, Category Fluency, and Digit Symbol-Coding tests; EQ-5D-5L; and CDR. Assessments administered to the study partner include the FAQ, ADCS-ADL, CDR, NPI, and RUD-Lite. Refer to Table 9.1 for the relative sequencing of tests for both patient and study partner. It is recommended that efficacy assessments be performed as the first activity of the study visits. Additionally, it is recommended that, during these visits, cognitive and functional tests are performed in the sequence 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 at all the visits to avoid the known circadian variation of cognitive performance (Higuchi et al 2000).

It is strongly recommended that patients and study partners 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 non-stressful study procedures may be conducted during these breaks.

Where there are multiple raters, i.e., a psychometric rater and a global rater, the recommended sequence of tests allows for simultaneous testing. Table 9.1 describes the testing flow and respective rater responsibilities in this situation.

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

Psychometric rater	Global rater
Patient	**Study partner**
1) MMSE	
2) RBANS	1) FAQ
3) ADAS-Cog_{13}	2) ADCS-ADL
4) Letter & Category Fluency tests	3) CDR[a]
5) Digit Symbol-Coding test	
6) EQ-5D-5L	
Study partner	**Patient**
4) NPI	7) CDR[a]
5) RUD-Lite	

All tests may not be administered at each visit; the relative order of tests is maintained for any tests that are administered at the same visit.

[a] The CDR must always be administered to the study partner first and then to the patient. It is recommended that both sections be administered on the same day.

Abbreviations: ADAS-Cog_{13} = 13-item Alzheimer's Disease Assessment Scale - Cognitive subscale; ADCS-ADL = The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; CDR = Clinical Dementia Rating; FAQ = Functional Activities Questionnaire; MMSE = Mini-mental State Examination; NPI = Neuropsychiatric Inventory; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RUD = Resource Utilization in Dementia.

9.1.5.2. Rater Qualifications and Blinding

Raters will be selected based on experience appropriate for the measures and will be trained so that variability in ratings is minimized. Two separate types of trained and qualified raters will administer the cognitive/functional and functional/global scales unless a single rater is approved by the sponsor. A psychometric rater will administer measures such as the MMSE, RBANS, ADAS-Cog_{13}, NPI, EQ-5D-5L, and RUD-Lite (see Table 9.1). A separate, global rater will administer the FAQ, the ADCS-ADL, and the CDR. If possible, the CDR should be administered by the same rater for a given patient. It is preferred that the same rater who administered the test in the feeder study also administer the tests for a given patient in Study AZFD.

Every effort should be made to prevent the CDR rater from becoming aware of any AEs the patient may experience during the study. Clinical Dementia Rating raters should, as much as possible, not have access to this information and should instruct patients and their study partners not to discuss AEs during the CDR interview. The rater should sign a statement to this effect on

the CDR worksheet. Site personnel who are involved in reviewing medical data or who may have access to AE information must refrain from discussing this information with the CDR rater.

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 ICF is signed, study site personnel will record via 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. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known, and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory, term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-protocol-mandated laboratory tests, vital sign measurements, ECG results, and other safety assessments should be reported as AE(s). Any new or aggravated, clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

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 discontinuation 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.

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 final disposition 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. Vasogenic Edema

If a patient develops symptoms believed to be 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, unless contraindicated. Study treatment should be discontinued if clinically significant symptomatic vasogenic edema occurs. Temporary discontinuation may be considered and study medication restarted if stable (see Section 8.1 for discontinuation from study treatment or Section 8.1.2 for temporary discontinuation). Temporary discontinuation of treatment may be considered if clinically significant symptomatic superficial siderosis or clinically significant symptomatic incident microhemorrhage is observed (Section 8.1.2 for temporary discontinuation). 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.

9.4.2. 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 may be obtained at the discretion of the dermatologist.
- A blood sample should be drawn for PK analysis (Section 9.5).
- 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.

9.4.3. Depression

In the event a patient experiences a clinically significant worsening of depression or a new onset major depression, the following procedures should be followed:

- The investigator or another qualified study physician should assess the patient clinically as soon as it is possible, and any appropriate emergency measures should be undertaken.
- Assuming an evaluation by a psychiatric emergency service is not required, the patient should be referred to a psychiatrist for an expert opinion.
- The investigator may initiate psychiatric management, including the use of psychiatric medication, as clinically needed.
- If study treatment is discontinued due to depression, the medical monitor should be notified as soon as possible, even if the event did not meet the definition of an SAE.

9.4.4. Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Gradual deterioration of cognition and/or function consistent with the usual course of AD should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as AEs during the study.

9.4.5. Laboratory Safety Assessment

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 should be reported to the Sponsor or its designee as an AE vie eCRF per Section 9.2.

9.4.6. Hepatic Monitoring

If a patient experiences AST or ALT ≥3X ULN, total bilirubin ≥2X ULN, or ALP ≥2X ULN, the investigator is to repeat relevant hepatic lab testing within 3 to 5 days, including ALT, AST, T. BIL, D. BIL, ALP, GGT, and CK, and to consult with the sponsor-designated medical monitor regarding collection of specific recommended clinical information via the HSCRFs and further follow-up laboratory tests.

Additionally, safety data should also be collected via the HSCRFs if the patient experiences a hepatic event considered to be a SAE. The process should be initiated by the investigator in consultation with the Sponsor-designated medical monitor. See Appendix 4.

9.4.7. Physical and Neurological Examinations

Complete physical examinations will be performed at baseline, and Visits 5, 11, 13, and 15 and at the ED visits indicated in the Schedule of Activities (see Section 2). Brief physical examinations will be performed at Visits 3, 7, 9, 12, and 14. 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 performed as indicated in the Schedule of Activities (see Section 2). The examinations will include a thorough assessment of gait, balance, coordination, cranial nerves, sensory and motor systems, and reflexes.

See Section 9.2 for information regarding the recording of AEs based on examinations.

9.4.8. Electrocardiograms

Digital 12-lead ECG files will be collected using continuous 12-lead digital recorders at the times indicated in the Schedule of Activities (see Table 2) after the patient has been resting in supine position for at least 10 minutes.

The 12-lead ECG equipment will be supplied and supported by the ECG central vendor. Electrocardiograms should be performed according to the study specific recommendations included in the ECG central vendor's Manual of Operations.

For each ECG time point shown in the Schedule of Activities, a 90-second continuous 12-lead digital ECG file will be collected. A 12-lead safety ECG will be printed at the site and the digital data will be transmitted to the ECG central vendor. The safety ECG data will be reviewed for quality and alerts by the central vendor, and this information will be transmitted back to the study site.

From the 90-second continuous ECG recording, the site will print a safety ECG that will be evaluated for heart rate and PR, RR, QRS, QT and QTcF intervals, and the investigator will judge the overall interpretation as normal or abnormal. 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, for immediate patient management, should any clinically relevant findings be identified. The recording date and time and the investigator interpretation (normal, abnormal clinically significant, abnormal not clinically significant) and the paper printouts will be stored as source documents. The investigator (or delegate) will evaluate the printout of the ECG in real time, with particular attention to the effects of clinical importance on the QRS and QTcF intervals.

The investigator may add and print extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason. In this event, concurrent blood samples may be collected for PK and electrolyte analyses. Additional ECGs may also be performed, at the discretion of the investigator, whenever a significant change in the patient's clinical status occurs (e.g., significant deterioration in cardiac, renal, or liver function or salt-water balance).

Safety ECG results should be reviewed by the investigator (or delegate) for potential clinical significance, and the clinical significance should be determined by the investigator in consultation with the cardiologist at the central vendor, if necessary. Note that new findings on ECG after enrollment that do not meet entry criteria do not automatically indicate that subject should be discontinued. In many cases discontinuation will not be necessary and will depend on clinical significance and implications (e.g., QTcF > 470 ms). See Section 9.2 for information regarding the recording of AEs based on ECG results.

9.4.9. Vital Signs

Vital signs, including supine and standing blood pressures and pulse rates, and temperature will be recorded at each in-clinic study visit (see the Schedule of Activities in Section 2).

See Section 9.2 for information regarding the recording of AEs based on tests and examinations.

9.4.9.1. Pulse Rate and Blood Pressure

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 the respective supine measurements, approximately 2 and 5 minutes after patient achieves a standing position.

9.4.9.2. Body Weight

Body weight will be measured in kilograms. Measurements should be taken without shoes and, when possible, the same scale should be used for all measurements.

9.4.10. Other Safety Assessments

9.4.10.1. Eye and Skin Examinations

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

Eye examination

A comprehensive eye examination, to include corrected visual acuity, intraocular pressure, a slit lamp examination, and a dilated fundus examination, will be performed at the times shown in the Schedule of Activities (Section 2). Note, patients with acute angle closure glaucoma or other contraindications to dilation should have a fundoscopic exam without dilation. The eye examinations must be supervised and reviewed and/or performed by an ophthalmologist or optometrist where permitted by local law.

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 supervised and reviewed and/or performed by a dermatologist.

The skin examinations will preferably be completed for a given patient by the same dermatologist who will inspect the patient's unclothed full body using a UV lamp.

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 hypopigmentation area (e.g., redness or induration). A static physician's global assessment will be used to determine the patient's overall hypopigmentation severity at a given time point 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 to be 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.

Data management and evaluation

Data from both the eye and skin examinations will be recorded on worksheets and then entered into the electronic data capture system at the primary study site in order to enable ongoing cumulative review and signal detection.

The ophthalmologist/optometrist or dermatologist will not make any determinations regarding whether the findings observed represent AEs or are causally related to the study medication and will not make decisions regarding whether the patient should discontinue study treatment. Instead, all information gathered by the ophthalmologist/optometrist or dermatologist should be reviewed by the site investigator, who will decide if an AE is present and who should take action, as appropriate.

See Section 9.2 for information regarding the recording of AEs based on examinations.

9.4.10.2. C-SSRS

The Columbia Suicide Severity Rating Scale (C-SSRS) will be performed to determine the presence of suicidality. The assessment schedule is indicated in the Schedule of Activities (see Section 2).

The C-SSRS is a unique, simple and short method of assessing both behavior and ideation that tracks all suicidal events and provides a summary of suicidality. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation and deterrents), all of which are significantly predictive of completed suicide.

If, during the performance of the C-SSRS assessment, the patient makes a statement indicating acute risk of suicide, the rater will immediately alert the site physician, and will stay with the

patient until the site physician is physically present. The site physician will then make a complete risk assessment and refer to or initiate treatment as required.

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.

If a suicide-related event is discovered *during the C-SSRS* but was not captured during the nonleading AE collection, sites should not change the AE form. If an event is serious or leads to discontinuation, this is an exception where the SAE and/or AE leading to discontinuation should be included on the AE form and the process for reporting SAEs should be followed.

9.4.10.3. Magnetic Resonance Imaging (Safety)

Magnetic resonance imaging will be used to monitor patients for amyloid-related imaging abnormalities (ARIA) evaluation (see Section 2).

Magnetic resonance imaging scanning will be conducted under the management of a central imaging vendor. The MRI scans will be acquired at imaging sites using a standardized protocol. Completion of the scheduled MRIs is required, unless a patient develops a contraindication to the MRI during the study.

The scans will be reviewed by the investigator or qualified designee for immediate patient management. Results of centrally read MRIs regarding patient care/safety will be reported back to the sites even though there was a local read. See Section 9.2 for information regarding the recording of AEs based on tests and examinations.

9.4.10.4. Safety Areas of Special Interest

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

- Adverse eye effects (see Section 9.4.10.1).
- Adverse skin effects including rash and hypopigmentation (see Sections 9.4.2 and 9.4.10.1).
- Peripheral nervous system, central nervous system and muscle effects (see Section 9.4.7).
- Liver toxicity (see Section 9.4.6).
- Cardiovascular (CV) -type events (including, but not limited to, orthostatic hypotension and QT prolongation; see Sections 9.4.8, 9.4.9, and 9.4.9.1).

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, e.g., 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 adjudication consultants and adjudicated as MACE events per a separate charter.

In the long-term follow-up of Year 2, MACE adjudications will continue at least until data lock for assessment of the primary analysis.

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

9.4.10.5. IDMC

The 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 and to ensure the integrity of the blinded nature of the study until data lock for assessment of the primary analysis. 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, additional analyses of the safety data may be conducted by the IDMC keeping the study team blinded.

9.5. Pharmacokinetics

Unscheduled venous blood samples to determine the plasma concentration of LY3314814 may occur in the event of rash, as part of the assessment of hepatic laboratory abnormalities, if abnormal findings are identified during ECG safety assessments, or as determined to be warranted by the sponsor. The date and time of the last dose of LY3314814 prior to PK collection should be recorded in the eCRF.

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

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 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, as an exploratory objective endpoint.

Samples collected to measure $A\beta_{1-40}$ and $A\beta_{1-42}$ will be identified by the patient number (coded) and will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the test run, or to retain the samples until the

end of the study to confirm that the results are valid. Samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.7. Genetics

9.7.1. Whole Blood Samples for Exploratory DNA and RNA Research

As part of an optional separate addendum, whole blood samples will be collected from consented patients for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) analysis as specified in the Schedule of Activities (Section 2) and separate addendum, where local regulations allow, as an exploratory objective endpoint.

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 DNA, RNA, proteins, lipids, and other cellular elements.

Plasma samples for non-pharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow. Additionally, as part of optional separate addenda, FDG and flortaucipir F 18 will be performed on consented patients as indicated in the Schedule of Activities.

Samples and images will be used for exploratory 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 ethical review boards (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 becomes commercially available.

9.8.1. Florbetapir PET (Positron Emission Tomography)

This study includes a longitudinal florbetapir F 18 amyloid PET scan for those patients who had a florbetapir F 18 PET scan at Visit 20 of Study AZES. Florbetapir F 18 amyloid PET will be used to evaluate changes in amyloid binding from baseline of Study AZES to the end of Year 1 of Study AZFD (Visit 11). See Schedule of Activities (Section 2). The number of florbetapir F 18 PET scans performed at Visit 11 may by limited at Sponsor discretion.

Florbetapir F 18 amyloid PET scanning will be conducted under the management of a central PET vendor. To meet the longitudinal florbetapir PET objective for Study AZFD, the central PET imaging vendor will quantitatively analyze the florbetapir F 18 scan obtained as part of Study AZFD by comparing it to the eligibility and follow up scans obtained as part of Study AZES.

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.

The details of data and images to be transferred are specified in the respective data and image transfer agreements.

9.8.2. Magnetic Resonance Imaging (Efficacy)

Magnetic resonance imaging scans will be obtained as described in Section 9.4.10.3 under the management of the central imaging vendor and transferred to the vendor for volumetric analysis.

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.

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 questionnaire (Wimo et al. 1998). In addition, health-related quality of life will be captured with the EQ-5D-5L. See Sections 9.1 and 9.1.3 for full scale descriptions.

The results of analyses of these variables may not be included in the CSR, but may be described in supplementary reports as appropriate.

10. Statistical Considerations

10.1. Sample Size Determination

It is estimated that approximately 1540 patients will complete Study AZES. Approximately 90% of these patients are expected to enroll in Study AZFD for an estimated total of approximately 1400 patients.

Study AZFD integrated with Study AZES forms a Delayed Start study (Study AZES-FD). Using the three stage hypothesis testing approach to delayed-start analysis as outlined in Liu-Seifert and colleagues (2015) and assuming a 5% ED rate in the first 6 months of Study AZFD and 10% ED rate in the first 12 months of Study AZFD, this sample size will provide approximately 81% power for the noninferiority test (i.e., 3rd hypothesis) for each dose when all patients have the opportunity to complete the 6 month time point at a one-sided alpha level of 0.1. At the 12 month time point of Study AZFD, this sample size will provide approximately 66% power for the noninferiority test.

These powering results are based on solanezumab Delayed-Start results of mild dementia, ApoE4 carriers (Studies LZAM, LZAN, and LZAO). 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. The 1540 patients estimated to complete Study AZES corresponds to an assumed ED rate of 30% from the original sample size of 2202. Extending to Study AZES-FD, the assumed ED rate until the 6 month time point of Study AZFD is 35%; until the end of the three years of Study AZES-FD, the assumed ED rate is 40%. We assume an approximate 10% annual dropout over the course of Study AZFD. These ED assumptions were used to adjust the randomized sample sizes using the following formula:

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

The effective sample size assumes that ED patients will contribute half the information that completing patients contribute. The effective sample sizes for the 6 month power calculation were 606 and 303, early-start arm and delayed-start arm, respectively; for 12 months, 588 and 294, 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 (2015), sig.level was set equal to 0.1 and alternative was set equal to “greater”.

10.2. Populations for Analyses of AZES-FD

For purposes of analysis, the following populations are defined:

Population	Description
Entered	All participants who sign informed consent in study AZES
Randomized	All entered patients who are randomized to treatment in Study AZES.
Evaluable (Intention-to-treat [ITT] analysis)	All randomized patients with an AZES 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 AZES 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.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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

Study AZES-FD offers the ability to assess disease modification of LY3314814 20 mg and LY3314814 50 mg. In order to present the integrated data, there will be four treatment regimens (see Table 10.1). The estimand of interest is to compare the disease progression across Study AZES-FD in all AZES randomized participants after 130 weeks attributable to randomized treatment.

Table 10.1. Treatment Regimens for Integrated Delayed-Start Study

Treatment Regimen	AZES Treatment	AZFD Treatment
1	LY 20 mg	LY 20 mg
2	LY 50 mg	LY 50 mg
3	Placebo	LY 20 mg
4	Placebo	LY 50 mg

Abbreviation: LY = LY3314814.

All Study AZES-FD analyses will follow the intent-to-treat (ITT) principle unless otherwise specified. Unless otherwise defined, a baseline measure is the last non-missing observation collected during Visits 1 and 2 of Study AZES. End point is the last non-missing post-baseline measurement in the Study AZES-FD. Efficacy analyses will be conducted on the Evaluable analysis set.

For mixed-model repeated-measures (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.

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 CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate.

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 AZES-FD 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

Baseline characteristics will be summarized for the randomized populations by Study AZES-FD 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

Concomitant medications are defined as those being taken on or after randomization (Visit 2 Study AZES). A summary of concomitant medications will be presented as frequencies and percentages for each treatment group in Study AZES-FD. 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 drug dictionary.

10.3.2.4. Treatment Compliance

The proportion of Study AZES-FD 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 Analyses

The primary analysis of Study AZES-FD is to test the delayed-start hypothesis to evaluate disease modification by LY3314814 as assessed by the ADAS-Cog_{13}. Comparisons are made by dose level between early-start patients (at the beginning of Study AZES) and delayed-start patients. Each comparison will evaluate three specific hypotheses described in the subsequent paragraph.

In the following description, the difference between an active arm and placebo at the end of Study AZES will be denoted Δ_1; the difference between delayed start and early start at the time point of interest in Study AZFD will be denoted Δ_2. Note that Δ_1 is the effect obtained from the primary analysis of Study AZES. The primary efficacy measure will be analyzed using estimates from MMRM models, in which three specific hypotheses are tested:

Test 1. Δ_1 is statistically significantly greater than 0.

Test 2. Δ_2 is statistically significantly greater than 0.

Test 3. 90% one-sided confidence limit of $\Delta_2 - 50\% \Delta_1$ is greater than 0.

The change from baseline (prior to the initiation of treatment in Study AZES) at each visit during Study AZES-FD (at the visits when the ADAS-Cog_{13} is assessed) will be the dependent variable.

The model for the fixed effects will include terms for: baseline ADAS-Cog_{13}, treatment, visit, treatment-by-visit interaction, baseline ADAS-Cog_{13} score-by-visit interaction, disease status at baseline (MCI due to AD or mild AD dementia), APOE4 status (carrier versus non-carrier), concomitant AChEI use at baseline (yes/no), age at baseline, and country. Visit will be considered a categorical variable with values equal to the visit numbers at which the scales were assessed.

The first hypothesis will be tested using an estimate of Δ_1 obtained from an MMRM model fit using data from all randomized subjects through week 104 (the end of Study AZES). The second hypothesis will be tested using an estimate of Δ_2 obtained from an MMRM including data from all randomized subjects through week 130 (26 week time point of Study AZFD).

The noninferiority margin for this hypothesis is specified as 50% of the treatment difference observed at the end of Study AZES. Using the same MMRM model used to test Δ_2, the hypothesis will be tested by constructing a 90% one-sided CI of the difference in least-squares means at the 26 week visit in Study AZFD (Visit 7). If the lower limit of the CI rules out the difference which would have been obtained if 50% of the observed difference had been lost, this study has provided evidence for modification of the course of AD beyond any short term symptomatic effects.

10.3.3.2. Multiplicity Adjustments

When testing the primary endpoint and each of the key secondary endpoints, Test 1 and Test 2 listed in the primary analysis section (Section 10.3.3.1) will be tested at the α level specified in the Study AZES multiplicity graph in a sequential approach.

All other pairwise tests of treatment effects will be conducted at a 2-sided alpha level of 0.025; 2-sided confidence intervals (CIs) will be displayed with a 97.5% CI. All tests of interactions between treatments and other factors will be conducted at an alpha level of 0.025.

Missing Data

A likelihood-based mixed effects model for repeated measures will be used to handle missing data. The model parameters are simultaneously estimated using restricted likelihood estimation incorporating all of the observed data. Estimates have been shown to be unbiased when the missing data are missing at random and when there is ignorable non-random missing data.

Repeated measures analyses will only use data from visits where the data was scheduled to be collected (see Andersen and Millen 2013). When subjects discontinue from the study early, there may be efficacy or safety data measurements at visits where the variables were not scheduled to be collected. These data will be used in all other analyses.

10.3.3.3. Secondary Analyses

Similar to the primary analysis, each of the key secondary efficacy outcomes (ADL, FAQ, MMSE, CDR-SB, and iADRS) will be assessed using the primary analysis and assessed up to 26 weeks (Visit 7). The model for each of these secondary analyses will include terms for: baseline efficacy score, treatment, visit, treatment-by-visit interaction, baseline efficacy score-by-visit interaction, disease status at baseline (MCI due to AD or mild AD dementia), APOE4 status (carrier versus non-carrier), concomitant AChEI use at baseline (yes/no), age at baseline, and country. The change from baseline (prior to the initiation of treatment in Study AZES) at each visit during Study AZES-FD (at the visits when the scale being analyzed is assessed) will be the dependent variable.

In addition, the Delayed-Start methodology will be used to analyze the ADAS-Cog_{13}, ADL, FAQ, MMSE, CDR-SB, and iADRS at the last scheduled visit (up to Week 104 [Visit 15] of Study AZFD) to evaluate the durability of the treatment effect.

10.3.3.4. 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 for the Study AZES-FD.

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

Plasma LY3314814 concentrations are not routinely measured in this study; there are no pre-specified analyses planned. If PK samples are collected due to the observation of an AE or abnormal finding (see Section 9.5), the relationship between the observation and LY3314814 plasma concentration may be explored.

10.3.6. Other Analyses

10.3.6.1. Health Economics

Precise statistical analyses to support health economics' objectives will be detailed in the SAP.

10.3.6.2. Subgroup Analyses

To assess the effects of various demographic and baseline characteristics, subgroup analyses will be performed based on disease severity at Study AZES baseline (mild AD dementia vs. MCI). All subgroup analyses will be considered exploratory.

10.3.7. Interim Analyses

While no formal interim analyses for efficacy and/or futility are planned for this study, if Study AZES and/or Study AZET are successful and a regulatory submission is created, available data from up to 26 weeks from this study will be analyzed and included in the submission.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
Aβ	amyloid beta peptide
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-Cog$_{13}$	13-item Alzheimer's Disease Assessment Scale-Cognition
ADCS-ADL	Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory
ADCS-iADL	Instrumental activities of the ADCS-ADL
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	amyloid-related imaging abnormality
AST	aspartate aminotransferase
AV	atrioventricular
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
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CV	cardiovascular
CYP3A4	cytochrome P450 3A4
DNA	deoxyribonucleic acid
ECG	electrocardiogram
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-5L™	A standardized instrument for use as a measure of health outcome (EuroQol Group; Rotterdam, The Netherlands)
ERB	Ethical Review Board
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)-N-methylbenzenamine)
GCP	good clinical practice
GMP	Good Manufacturing Practice
HSCRF	Hepatic Safety Case Report Form
iADRS	integrated Alzheimer's Disease Rating Scale
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for 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	intent 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)

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
MACE	major adverse CV event
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
QTcF	QT interval adjusted for heart rate using the Fridericia formula
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBC	red blood cells
RNA	ribonucleic acid
RUD-Lite	Resource Utilization in Dementia-Lite
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.
SHFU	Self-Harm Follow-Up
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin level
ULN	upper limit of normal

VAS	visual analog scale
vMRI	volumetric magnetic resonance imaging
WBC	white blood cells

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Variables

Hematology(blood)	**Clinical Chemistry (serum)**
Hematocrit	Alanine aminotransferase (ALT)
Hemoglobin	Albumin
Leukocytes (WBC) count	Alkaline phosphatase
Absolute leukocyte differential count (neutrophils, basophils, monocytes, eosinophils and lymphocytes)	Aspartate aminotransferase (AST)
	Bilirubin, total
Platelet count	Blood urea nitrogen (BUN)
	Calcium, total
Electrolytes (serum)	C-reactive protein
Bicarbonate	Creatine kinase (CK)
Chloride	Creatinine
Phosphate	Glucose (random)
Potassium	
Sodium	**Endocrinology**
	Thyroid-stimulating hormone[a]
Urinalysis	Total thyroxine[a]
Blood	
Color	**Other**
Glucose	Hemoglobin A1c (HbA1c)[a]
Ketones	
Leukocyte esterase	
pH	
Protein	
Specific gravity	

Abbreviation: WBC = white blood cells.

[a] At Visit 11, and Visit 15 or ED only.

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 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 9.4.5 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.

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 Council for 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.

Case report form data collected by a third-party will be encoded by the third-party and stored electronically in the third-party's database system. Validated data will subsequently be transferred to the Lilly data warehouse, using standard Lilly file transfer processes.

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 Lilly data warehouse.

Data from complaint forms submitted to Lilly 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 Lilly, or its designee, clinical research physician.

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
Eosinophils	Epstein-Barr virus VCA antibody, IgG and IgM[c]
Basophils	Hepatitis A antibody, total
Platelets	Hepatitis A antibody, IgM
	Hepatitis B surface antigen
	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	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin
PK for LY3314814	**antibody)[a]**
	Type I anti-liver kidney microsomal antibodies

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; 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 Lilly-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. Protocol Amendment I8D-MC-AZFD(a) Summary A Randomized, Double-Blind, Delayed-Start Study of LY3314814 (AZD3293) in Early Alzheimer's Disease Dementia (Extension of Study AZES, The AMARANTH Study)

Overview

Protocol I8D-MC-AZFD A Randomized, Double-Blind, Delayed-Start Study of LY3314814 (AZD3293) in Early Alzheimer's Disease Dementia (Extension of Study AZES, The AMARANTH Study) has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Amendment Summary for Protocol I8D-MC-AZFD Amendment (a)

Section # and Name	Description of Change	Brief Rationale
Section 1. Synopsis	Added in Year 2 extension time points to include the delayed-start analyses in the Objective/Endpoint table, Summary of Study Design, and Treatment Arms and Duration Sections	Extending the study 1 additional year from original protocol
Section 1. Synopsis Section 4. Objectives and Endpoints	Added CDR-SB and updated functional score to ADCS-ADL as secondary endpoints	Moving CDR-SB from an exploratory to secondary endpoint and including all ADCS-ADL score items, not just instrumental items (iADL)
Section 2. Schedule of Activities	Added in Year 2 to Schedule of Activities and updated footnotes accordingly	Extending the study 1 additional year from original protocol
Section 2. Schedule of Activities	Added footnote e	Clarification that there might be a delay in starting Visit 12 for patients who complete the first year of the protocol before the amendment is approved
Section 2. Schedule of Activities	Added footnote i	Clarification of early discontinuation procedures for certain measures
Section 3.1 Study Rationale	Added in Year 2 time points of the delayed-start analyses	Extending the study 1 additional year from original protocol
Section 4. Objectives and Endpoints	Added in Year 2 extension time points to include the delayed-start analyses	Extending the study 1 additional year from original protocol
Section 5.1. Overall Design	Added in statement regarding the Visit 12 initation window to be consistent with new footnote e in the Schedule of Activities	Clarification that there might be a delay in starting Visit 12 for patients who complete the first year of the protocol before the amendment is approved
Section 5.1. Overall Design	Updated Study Design figure to include Year 2 and the symptomatic treatment windows	Extending the study 1 additional year from original protocol
Section 5.2 Number of Participants	Added statement about consent	Clarification that consent for Study AZFD may be obtained any time prior to performing procedures specific to this study.
Section 5.3 End of Study Definition	Added that final study visit will occur approximately 110 weeks after the last patient completes the feeder study	Extending the study 1 additional year from original protocol, plus approximately 6 weeks of follow-up
Section 5.4 Scientific Rationale for Study Design	Added in Year 2 extension time point	Extending the study 1 additional year from original protocol
Section 6.1 Inclusion Criteria	Updated wording of Inclusion Criteria #2	Clarification of which patients who participate

		through Visit 20 of Study AZES are eligible to enroll in Study AZFD
Section 7.2.1 Selection and Timing of Doses	Added a note regarding transition from Study AZES to Study AZFD	Want to minimize gaps in treatment
Section 7.7.1 Initiation of Post-Randomization Symptomatic AD Treatments	Added in Year 2 time points to be consistent with updated Study Design figure	Extending the study 1 additional year from original protocol
Section 7.8.2 Continued Access	Updated wording related to continued access	Clarification that continued access can only be provided within an approved protocol.
Section 8.1.2 Temporary Discontinuation from Study Treatment	Added in "per study year"	Clarification that the maximum cumulative permissible treatment suspension is 3 weeks per year
Section 8.2 Discontinuation from the Study	Added reasons for discontinuation	Clarification that patients who discontinue the study early, for any reasons including early study termination as determined by the Sponsor and/or IDMC, will have ED procedures performed
9.1.2 Secondary Efficacy Assessments	Added CDR-SB and updated functional score to ADCS-ADL as secondary endpoints	Moving CDR-SB from an exploratory to secondary endpoint and including all ADCS-ADL score items, not just instrumental items (iADL)
9.1.2 Secondary Efficacy Assessments	Updated maximum score values for ADCS-bADL, ADCS-iADL, and iADRS	Change in classification of questions 6a and 6b of ADCS-ADL between basic and instrumental items.
9.4.1 Vasogenic edema	Added wording to vasogenic edema safety section	Clarification of when temporary discontinuation would be considered due to vasogenic edema
9.4.7 Physical and Neurological Examinations	Added in Year 2 time points for these measures	Extending the study 1 additional year from original protocol
Section 9.4.10.4 Safety Areas of Special Interest	Added wording that MACE adjudications will continue at least until data lock for assessment of the primary analysis	Clarification of long-term follow-up when extending the study 1 additional year from the original protocol
Section 9.8.1 Florbetapir PET	Added wording regarding the number and timing of florbetapir F 18 PET scans performed	Clarification that florbetapir F 18 PET scans will not be conducted in the extension Year 2
Section 10.1 Sample Size Determination	Added wording regarding the estimated discontinuation rate	Clarification that the estimated annual discontinuation rate is approximately 10%
Section 10.3.3.2 Multiplicity Adjustments	Updated wording to minimize redundancy from other sections	Clarification of statistical methods for multiplicity adjustments
Section 10.3.3.3 Secondary Analyses	Added in Year 2 time points of the delayed-start analyses; added CDR-SB and updated functional	Extending the study 1 additional year from original protocol; consistency with new objectives/endpoint

	score to ADCS-ADL as secondary endpoints	table.
Appendix 2. Clinical Laboratory Tests	Updated timing to clinical laboratory testing	Updated the collection times for total thyroxine, thyroid stimulating hormone, and hemoglobin A1c to include assessments at Visits 15.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

1. Synopsis

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • The primary analysis of Study AZES-FD is to evaluate disease modification as outlined in Liu-Seifert (2015). This will be accomplished by testing the three delayed-start hypotheses in both doses of LY3314814 across Study AZES and up to Week 26 (Visit 7) of Study AZFD.	• ADAS-Cog$_{13}$
Secondary *Clinical efficacy objective:* • To evaluate the disease modification of both doses of LY3314814 on functional and cognitive outcomes across Study AZES and up to Week 26 (Visit 7) of Study AZFD using the primary analysis methodology.	• Functional Outcome Measures o ADCS-~~i~~ADL score o FAQ • Cognitive/Functional Outcome Measures o iADRS score o CDR-SB • Cognitive Outcome Measures o MMSE
• The delayed-start analyses as outlined above will also be examined through Week 104 (Visit 15) for cognitive and functional outcomes.	• ADAS-Cog$_{13}$, ADCS-~~i~~ADL, FAQ, iADRS, CDR-SB, MMSE
Safety Objective • Collect information in order to further characterize the safety and tolerability of LY3314814 in patients with early AD dementia (at the time of entry into Study AZES)	• 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 Columbia-Suicide Severity Rating Scale (C-SSRS)

Abbreviations: AD = Alzheimer's disease; ADAS-Cog_{13} = 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-~~i~~ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory ~~instrumental items score~~; AE = adverse event; CDR-SB = Clinical Dementia Rating Sum of Boxes; ECG = electrocardiogram; FAQ = Functional Activities Questionnaire; iADRS = integrated Alzheimer's Disease Rating Scale; ~~CDR-Global Score = Clinical Dementia Rating Global Score; NPI = Neuropsychiatric Inventory;~~ MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging.

Summary of Study Design:

Study I8D-MC-AZFD is a multicenter, randomized, double-blind, ~~52~~104-week delayed-start study with 2 fixed doses of LY3314814 in patients diagnosed with early AD, which is defined as the continuum of patients with MCI-AD and patients diagnosed with mild dementia of the Alzheimer's type (mild AD dementia), at the time of entry into feeder Study AZES.

Treatment Arms and Duration:

In Study AZFD, all patients will receive treatment with LY3314814. Patients who were randomized to LY3314814 in feeder Study AZES will continue with the same drug dose in Study AZFD. Patients who were randomized to placebo in the feeder study will be randomized, in a 1:1 ratio, to either LY3314814 20 mg or LY3314814 50 mg. All patients will receive study drug for ~~52~~ 104 weeks.

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2. Schedule of Activities

Study procedure[a]												ED[e]	F/U
Visit number	V20-AZES/ V1-AZFD[b]	V2	V3	V4	V5	V6	V7	V8[d]	V9	V10	V11		V801[e]
Study week		1	4	7	13	19	26	32	39	45	52		
Tolerance interval for Visit (days)		±3	±3	±7	±7	±7	±7	±7	±7	±7	±10		
Informed consent	X												
Randomization	X												
Prior/concomitant treatments	CO	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X												
NIA-AA criteria review										X		X	
FAQ	CO						X				X	X	
ADCS-ADL	CO						X				X	X	
CDR[f]	CO						X				X	X	
MMSE	CO				X		X				X	X	
RBANS										X		X	
ADAS-Cog$_{13}$	CO				X		X				X	X	
NPI	CO						X				X	X	
Letter & Category Fluency, Digit Symbol-Coding tests	CO						X				X	X	
EQ-5D-5L (patient)	CO					X				X		X	
RUD-Lite	CO					X				X		X	
MRI	CO										X	X	
Florbetapir F18 Amyloid PET[g]	CO										X	X[g]	
Required blood samples for plasma biomarkers[h]							X[h]				X[h]	X[h]	
Laboratory tests[i]	CO		X	X	X		X		X		X	X	
Physical, neurological examinations	CO		X[j]		X		X[j]		X[j]		X	X	
Comprehensive eye examination	CO										X	X	
Skin examination	CO				X						X	X	
Vital signs[k]	CO	X	X	X	X	X	X		X	X	X	X	X
Body weight	CO				X		X				X	X	
12-lead ECG[l]	CO	X	X		X		X		X		X	X	X

Study procedure[a]												ED[c]	F/U
Visit number	V20-AZES/ V1-AZFD[b]	V2	V3	V4	V5	V6	V7	V8[d]	V9	V10	V11		V801-[e]
Study week		1	4	7	13	19	26	32	39	45	52		
Tolerance interval for Visit (days)		±3	±3	±7	±7	±7	±7	±7	±7	±7	±10		
C-SSRS and Self-Harm Supplement Form[m]	CO	X	X	X	X	X	X		X	X	X	X	X
Dispense drug	X	X	X	X	X	X	X		X	X			
Assess drug compliances[n]		X	X	X	X	X	X	X[n]	X	X	X	X	
Adverse events	CO	X	X	X	X	X	X	X	X	X	X	X	X
Optional Addenda (site and patient specific)													
Fluorodeoxyglucose (FDG) PET[o]	CO										X	X[p]	
or Flortaucipir F 18 (^{18}F-AV-1451) PET[o]	CO										X	X[p]	
Consent for optional DNA/RNA blood sample[q]	X[q]												
Blood sample for DNA[r] (optional)							X					X[s]	
Blood sample for RNA[r] (optional)							X				X	X[s]	

Study procedure[a]	Delayed-Start Year 1											Delayed-Start Year 2				ED[eb]	F/U
Visit number	V20-AZES/ V1-AZFD[bc]	V2	V3	V4	V5	V6	V7	V8[d]	V9	V10	V11	V12[e]	V13	V14	V15		V801[ef]
Study week		1	4	7	13	19	26	32	39	45	52	65	78	91	104		
Tolerance interval for Visit (days)		±3	±3	±7	±7	±7	±7	±7	±7	±7	±10	±7	±7	±7	±7		
Informed consent	X																
Randomization	X																
Prior/concomitant treatments	CO	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X																
NIA-AA criteria review										X				X		X	
FAQ	CO						X				X		X		X	X	
ADCS-ADL	CO						X				X		X		X	X	
CDR[fg]	CO						X				X		X		X	X	
MMSE	CO				X		X				X		X		X	X	
RBANS										X				X		X	
ADAS-Cog$_{13}$	CO				X		X				X		X		X	X	
NPI	CO						X				X		X		X	X	
Letter & Category Fluency, Digit Symbol-Coding tests	CO						X				X		X		X	X	
EQ-5D-5L (patient)	CO					X				X					X	X	
RUD-Lite	CO					X				X					X	X	
MRI	CO										X				X	X	
Florbetapir F18 Amyloid PET[gh]	CO										X					X[gi]	
Required blood samples for plasma biomarkers[hj]							X[hj]				X[hj]					X[hi,j]	
Laboratory tests[ik]	CO		X	X	X		X		X		X	X	X	X	X	X	
Physical, neurological examinations	CO		X[jl]		X		X[jl]		X[jl]		X	X[jl]	X	X[jl]	X	X	
Comprehensive eye examination	CO										X				X	X	
Skin examination	CO				X						X				X	X	
Vital signs[km]	CO	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Body weight	CO				X		X				X				X	X	
12-lead ECG[in]	CO	X	X		X		X		X		X		X		X	X	X
C-SSRS and Self-Harm Supplement Form[mo]	CO	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X

Study procedure[a]	Delayed-Start Year 1											Delayed-Start Year 2				ED[eb]	F/U
Visit number	V20-AZES/ V1-AZFD[bc]	V2	V3	V4	V5	V6	V7	V8[d]	V9	V10	V11	V12[e]	V13	V14	V15		V801[ef]
Study week		1	4	7	13	19	26	32	39	45	52	65	78	91	104		
Tolerance interval for Visit (days)		±3	±3	±7	±7	±7	±7	±7	±7	±7	±10	±7	±7	±7	±7		
Dispense drug	X	X	X	X	X	X	X		X	X	X	X	X	X			
Assess drug compliances[np]		X	X	X	X	X	X	X[n]	X	X	X	X	X	X	X	X	
Adverse events	CO	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
~~Fluorodeoxyglucose (~~FDG~~)~~ PET[eq] *or* Flortaucipir F 18 ~~(~~^{18}~~F-AV-1451)~~-PET[eq]	CO										X					X[pr,i]	
	CO										X					X[pr,i]	
Consent for optional DNA/RNA blood sample[qs]	X[qs]																
Blood sample for DNA[rt] (optional)							X									X[su]	
Blood sample for RNA[rt] (optional)							X				X					X[si]	

Abbreviations: ADAS-Cog = 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; CO = Carryover; ~~CSF = Cerebrospinal fluid;~~ C-SSRS = Columbia Suicide Severity Rating Scale; DNA= deoxyribonucleic acid; ~~DSM-V = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition;~~ ECG = electrocardiogram; ED = early discontinuation; EQ-5D-5L (patient) = 5-dimensional EuroQol quality of life scale; FAQ = Functional Activities Questionnaire; FDG = fludeoxyglucose; F/U = follow-up; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NIA-AA = National Institute of Aging – Alzheimer's Association; NPI = Neuropsychiatric Inventory; PET = positron emission tomography; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RNA = ribonucleic acid; RUD-Lite = Resource Utilization in Dementia-Lite; V = visit.

[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 (i.e., visits should be scheduled based on the randomization date rather than the previous visit). Even if a patient enters into Study AZFD, it is expected that the patient complete all Study AZES procedures. Any missing procedures should be completed during the maximum time window of the Study AZES follow-up period (6 weeks). Studies AZES and AZFD are considered compatible studies.

~~[b] First dose to be administered the day after completion of Visit 1, preferably in the morning.~~

[eb] All patients who discontinue study treatment before Visit ~~11~~ 15 should have Early Discontinuation (ED) procedures and assessments performed as soon as possible. ADCS-ADL, FAQ, CDR, MMSE, RBANS, ADAS-Cog$_{13}$, NPI, and Letter & Category Fluency, Digit Symbol-Coding tests should be conducted at the early discontinuation visit if it has been more than 12 weeks since they were last administered. ~~Imaging assessments such as~~If it has been >6 months since the last- MRI, then ~~should have~~an -MRI is performed~~. during the ED visit~~. ~~and~~ PET scans (applicable to a subset of patients) should be performed if discontinuation occurs between ~~after~~ Visit 6 and Visit 11.

[bc] First dose to be administered the day after completion of Visit 1, preferably in the morning.

[d] Visit 8 is conducted by telephone and may include either the patient or the study partner, or both, as appropriate. The patient or study partner may be required to visit the clinic if drug dispensing is needed.

[e] The initiation of Visit 12 may be delayed for the patients who have completed the first year of the protocol prior to regulatory and ethics approval of the protocol amendment that includes the Year 2 extension.

[ef] Patients who complete study treatment ~~at Visit 11~~ or have early discontinuation should participate in a follow-up visit (Visit 801), 4 to 6 weeks after the last dose of study treatment.

[fg] 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 approximately the same time of day at designated study visits, if possible.

[gh] Assessment performed only for those patients who had florbetapir F 18 PET scan at Visit 20 in Study AZES. Patients with current participation in a research and/or medical protocol involving PET ligands or radioactive agents judged not to be scientifically or medically compatible with this study, with exposure to ionizing radiation that in combination with the planned administration of study florbetapir PET ligand would result in a cumulative exposure that exceeds local recommended exposure limits, or hypersensitivity to the active substance or any of the excipients of florbetapir F 18 are excluded from obtaining the florbetapir PET scan.

[i] If discontinuation occurs after Visit 11, it is not collected or performed.

[hj] Blood samples for determination of plasma biomarkers ($A\beta_{1\text{-}40}$, $A\beta_{1\text{-}42}$) will preferably be collected 2 to 3 hours post-dose at indicated visits and failure to collect within this time frame will not be considered a protocol deviation. Blood samples for other exploratory plasma biomarkers will also be collected at indicated visits.

[ik] Hematology, clinical chemistry, electrolytes, and urinalysis are included in every laboratory determination. Thyroid-stimulating hormone, total thyroxine and hemoglobin A1c will be measured at Visits 11, and 15~~11~~ or ED.

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

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

[ln] Single safety ECGs are required.

[mo] The Adult C-SSRS Since Last Visit version will be 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 (SHFU) form will be used to collect additional information to allow for a more complete assessment of these behaviors.

[np] 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. During visits conducted by telephone, the patient or study partner will be questioned about compliance with study treatment.

[oq] Patients who participated in Study AZES FDG PET or flortaucipir F 18 PET addenda will have the option to continue in the addendum to which they were previously assigned, provided that they consent for these procedures in Study AZFD.

[pr] If the patient discontinues study treatment betweenafter Visit 6 and Visit 11, the FDG or flortaucipir F 18 addendum PET scan should be performed.

[qs] Participation in this procedure is optional and consent can occur any time before blood draw.

[rt] Patients who participate in optional pharmacogenomics samplings will be provided a separate informed consent for the samplings. Failure to participate in optional sampling will have no influence on the eligibility of the patient for the study. Consent can be obtained any time before blood draw.

[su] Blood sample should be collected at ED visit if the patient discontinues prior to Visit 7.

3. Introduction

3.1. Study Rationale

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LY3314814 is being developed for the modification of the clinical course of Alzheimer's disease (AD) by slowing disease progression in patients diagnosed with early AD, which is defined as the continuum of patients with mild cognitive impairment due to AD (MCI-AD) and patients diagnosed with mild dementia of the Alzheimer's type (mild AD dementia) randomized to Study AZES. Study I8D-MC-AZFD will test the hypothesis that patients originally randomized to receive placebo in the double-blind feeder Study AZES and switched to LY3314814 at the start of Study AZFD do not "catch up" on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog_{13}) at Week 26 (Visit 7) of Study AZFD to patients originally randomized to receive LY3314814 in the double-blind feeder Study AZES. Additionally, secondary delayed-start analyses will also be conducted over the entire 104 weeks of treatment. Data acquired will also be used to evaluate the long-term safety and efficacy profile of LY3314814.

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4. Objectives and Endpoints

Table 4.1 shows the objectives and endpoints of the study.

Table 4.1. Objectives and Endpoints

Objectives	Endpoints
Primary • The primary analysis of Study AZES-FD is to evaluate disease modification as outlined in Liu-Seifert (2015). This will be accomplished by testing the three delayed-start hypotheses in both doses of LY3314814 across Study AZES and up to Week 26 (Visit 7) of Study AZFD.	• ADAS-Cog_{13}
Secondary *Clinical efficacy objective:* • To evaluate the disease modification of both doses of LY3314814 on functional and cognitive outcomes across Study AZES and up to Week 26 (Visit 7) of Study AZFD using the primary analysis methodology.	• Functional Outcome Measures o ADCS-~~i~~ADL score o FAQ • Cognitive/Functional Outcome Measures o iADRS score o CDR-SB • Cognitive Outcome Measures o MMSE
• The delayed-start analyses as outlined above will also be examined through Week 104 (Visit 15) for cognitive and functional outcomes.	• ADAS-Cog_{13}, ADCS-~~i~~ADL, FAQ, iADRS, CDR-SB, MMSE

Objectives	Endpoints
Safety Objective • Collect information in order to further characterize the safety and tolerability of LY3314814 in patients with early AD dementia (at the time of entry into Study AZES)	• 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 Columbia-Suicide Severity Rating Scale (C-SSRS)

Abbreviations: AD = Alzheimer's disease; ADAS-Cog_{13} = 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-~~i~~ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory ~~instrumental items score~~; AE = adverse event; CDR-SB = Clinical Dementia Rating Sum of Boxes; ECG = electrocardiogram; FAQ = Functional Activities Questionnaire; iADRS = integrated Alzheimer's Disease Rating Scale; ~~CDR-Global Score = Clinical Dementia Rating Global Score; NPI = Neuropsychiatric Inventory;~~ MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging.

5. Study Design

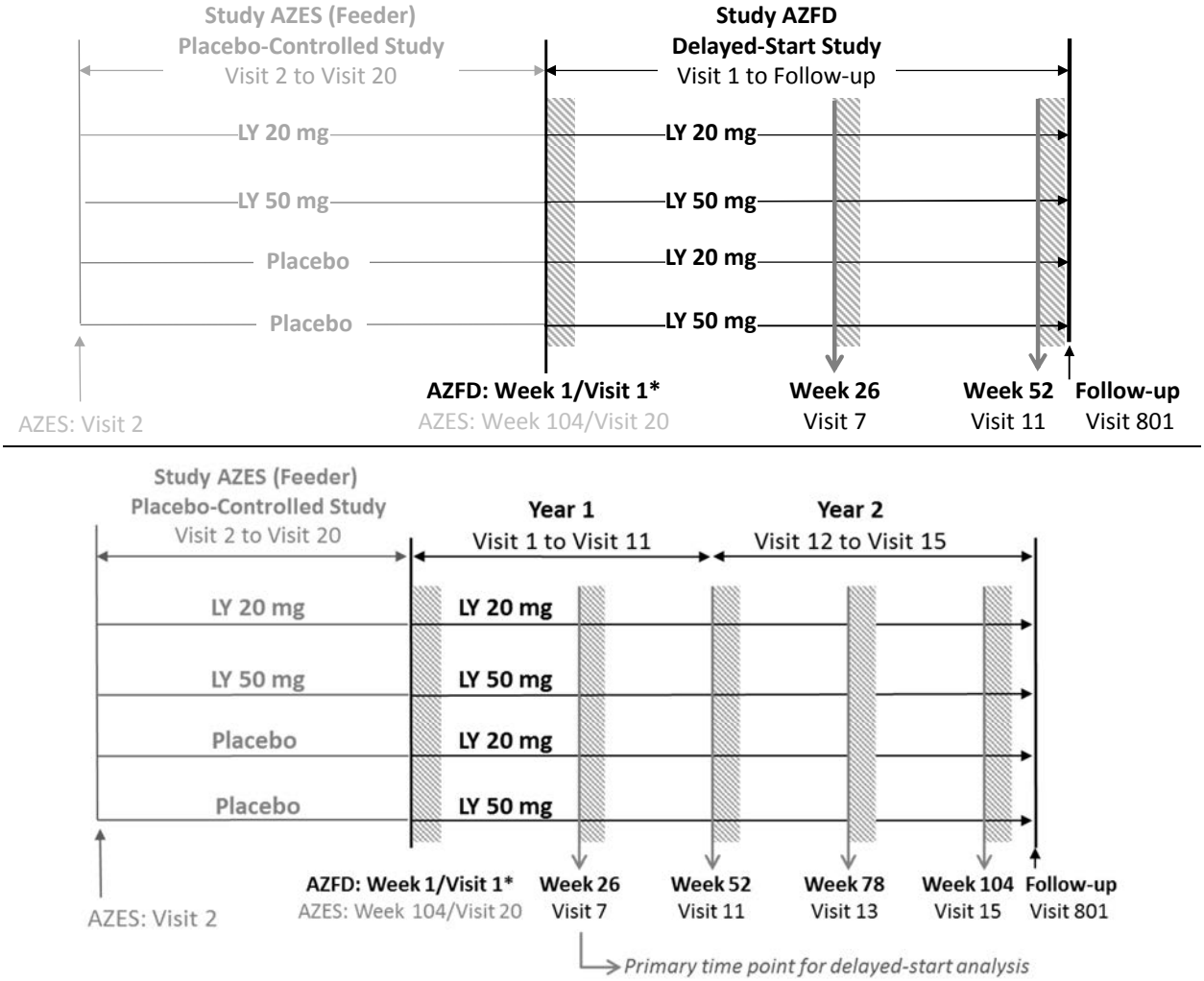
5.1. Overall Design

Study AZFD is a multicenter, randomized, parallel-group, double-blind, ~~52~~104-week-long study of 2 fixed dose levels of LY3314814 in patients with early AD at the time of enrollment into the feeder Study AZES. The actual number of patients to be enrolled is dependent on the number of eligible patients completing feeder Study AZES.

The treatment period of this delayed-start extension will begin at the conclusion of Visit 20 of the feeder Study AZES which will also serve as Visit 1 for Study AZFD, and will continue with 104~~52~~ weeks of treatment. Patients who were randomized in Study AZES to either 20 mg or 50 mg of LY3314814 will continue on the treatment allocation from the feeder study. Patients randomized to placebo in Study AZES will be randomized in a blinded fashion 1:1 to LY3314814 20 mg or 50 mg daily (QD), administered orally. Neither the patient nor investigator will be unblinded to feeder study treatment assignments. Assessments will be made as indicated on the Study Schedule of Activities found in Section 2.

The study includes a longitudinal florbetapir F 18 amyloid positron emission tomography (PET) scan for those patients who had a florbetapir F 18 PET scan at Visit 20 of Study AZES. In addition, there are two longitudinal addenda of fluorodeoxyglucose (FDG) PET and ^{18}F-AV-1451 PET at applicable sites. Patients who participated in these addenda in Study AZES are eligible to participate in the respective addenda in Study AZFD. Figure 5.1 illustrates the study design.

The initiation of Visit 12 may be delayed for the patients who have completed the first year of the protocol prior to regulatory and ethics approval of the protocol amendment that includes the Year 2 extension.



Abbreviation: LY = LY3314814.

* At Visit 1 of Study AZFD (Visit 20 of Study AZES), patients randomized to placebo from Study AZES will be randomized 1:1 to LY 20 mg or LY 50 mg in Study AZFD.

Note: Gray boxes after Study AZFD Visits 1, 7, ~~and~~ 11, 13, and 15 indicate the 4-week symptomatic treatment initiation window for subjects with progression of symptoms.

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

5.2. Number of Participants

It is estimated that approximately 1540 participants will complete the feeder Study AZES. Based on historical data, it is assumed that 90% (approximately 1400) of the participants from Study AZES will provide consent to continue participation in Study AZFD. Consent for Study AZFD may be obtained at any time prior to performing procedures specific only for Study AZFD.

5.3. End of Study Definition

The end of the study is defined as "the last visit of the last patient undergoing the study." This definition applies to the entire study and is not region specific.

The study is expected to start in Q1 of 2017 which is the scheduled date for the first completers of the feeder Study AZES. The final study visit will occur approximately 110 ~~58~~ weeks after the last patient completes the feeder study.

5.4. Scientific Rationale for Study Design

Study AZFD integrated with Study AZES forms a Delayed Start study design. Data from randomization (Visit 2) in Study AZES through Visit 7 of Study AZFD will be used to test whether there is a treatment effect that cannot be achieved with a later start of treatment. The time points beyond the primary analysis at 26 weeks (Visit 7) in Study AZFD will be analyzed upon last patient visit to determine the robustness of early treatment over the full 104~~52~~-week delayed-start period.

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6. Study Population

6.1. Inclusion Criteria

General Inclusion Criteria

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

[2] Patients ~~completing~~participating through Visit 20 of Study AZES and who have not permanently discontinued study treatment. Note: Patients who have permanently discontinued study treatment prior to Visit 20 of Study AZES and have remained in Study AZES off treatment are not eligible for Study AZFD.

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7. Treatments

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7.1.1. Packaging and ~~Labelling~~Labeling

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All kits will bear a label 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~~labeling.

…

7.2.1. Selection and Timing of Doses

Patients will continue on Study AZES study treatment during the entire period of Visit 20 of Study AZES. To ensure that patients continue on study treatment without a lapse in therapy, patients will take their last dose of Study AZES treatment on the day of randomization into Study AZFD. Since many of the procedures and assessments will be used for both study visits, Visit 20 of Study AZES will occur simultaneously with Visit 1 of Study AZFD. Once all other AZES Visit 20 assessments and procedures have been completed, the final procedure in Study AZES is to assess drug compliance and collect any unused AZES study medication. After resolving Study AZES drug compliance, the patient can be randomized to the Study AZFD treatment. Patients are to take the first dose of Study AZFD treatment on the day following randomization into the study. The dose is to be taken once daily, preferably in the morning unless instructed otherwise.

Note: Every attempt should be made to ensure that the transition from Study AZES to Study AZFD is seamless. Any gaps in treatment should be minimized. If a gap in treatment occurs, please notify your Clinical Research Associate for Study AZFD.

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7.7.1. Initiation of Post-Randomization Symptomatic AD Treatments

Over the period of this trial patients may have progression of symptoms/disease (patients may progress to mild or moderate/severe stages of disease). For patients for whom treatment becomes medically indicated during the trial, initiation of cholinesterase inhibitors and memantine (moderate stages) is permitted. This initiation must only occur when medically indicated and documenting the rationale or indication for initiation will be required. In order to adequately capture any decline as well as stable improvements, these symptomatic treatments should be initiated within approximately four weeks after the completion of cognitive testing at the Visit 1, Visit 7, ~~and~~ Visit 11, Visit 13, and Visit 15 (see Figure 5.1). Initiation at a time outside of these windows is discouraged, but the Sponsor-designated medical monitor should be contacted if a clinical need arises outside of the protocol-specified windows and will not be deemed a protocol violation if approved.

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7.8.2. Continued Access

~~LY3314814 may be made available to patients who have completed the study and are still receiving benefit from study treatment until LY3314814 becomes commercially available in the~~

~~host country of the patient.~~ Continued access would only be provided through a regulatory and IRB-approved protocol, where applicable. Safety and efficacy data may be collected during this time period.

8. Discontinuation Criteria

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8.1.2. Temporary Discontinuation from Study Treatment

Treatment suspension and re-dosing of study drug can be considered based on the Principal Investigator's judgment (examples include short-term treatment using a prohibited drug, uncertain adverse event, hospitalization). The maximum cumulative permissible treatment suspension during the course of Study AZFD is 3 weeks per study year over the duration of the study. Temporary treatment discontinuation and restarting needs to be documented. If temporary discontinuation is due to an AE, it should be reported to the Sponsor-designated medical monitor.

8.2. Discontinuation from the Study

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Patients who discontinue the study early (for any reason, including early study termination as determined by the Sponsor and/or IDMC) will have ED 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.

…

9. Study Assessments and Procedures

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9.1.2. Secondary Efficacy Assessments

Secondary efficacy variables in this study are the changes from baseline in Study AZES to Week 26 (Visit 7) in Study AZFD in FAQ score, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory ~~instrumental items score~~ (ADCS-~~i~~ADL), integrated Alzheimer's Disease Rating Scale (iADRS), CDR-SB, and Mini-Mental State Examination (MMSE).

…

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~~19, and the maximum instrumental items score (sum of individual instrumental item scores) is ~~56~~ 59 (Galasko et al. 2004).

…

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 to ~~141~~144; 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).

Administration of the CDR 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

…

~~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).~~

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

…

9.4.1. Vasogenic Edema

If a patient develops symptoms believed to be 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, unless contraindicated. Study treatment should be discontinued if clinically significant symptomatic vasogenic edema occurs. Temporary discontinuation may be considered and study medication restarted if stable (see Section 8.1 for discontinuation from study treatment or Section 8.1.2 for temporary discontinuation). Temporary discontinuation of treatment may be considered if clinically significant symptomatic superficial siderosis, or clinically significant symptomatic incident microhemorrhage is ~~seen~~observed (~~see Section 8.1 for discontinuation from study treatment~~Section 8.1.2 for temporary discontinuation). 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.

…

9.4.7. Physical and Neurological Examinations

Complete physical examinations will be performed at baseline, and Visits 5~~ and,~~ 11, 13, and 15, and at the ED visits indicated in the Schedule of Activities (see Section 2). Brief physical

examinations will be performed at Visits 3, 7, ~~and~~ 9, 12, and 14. 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).

…

9.4.10.4. Safety Areas of Special Interest

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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, e.g., 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 adjudication consultants and adjudicated as MACE events per a separate charter.

In the long-term follow-up of Year 2, MACE adjudications will continue at least until data lock for assessment of the primary analysis.

…

9.8.1. Florbetapir PET (Positron Emission Tomography)

This study includes a longitudinal florbetapir F 18 amyloid PET scan for those patients who had a florbetapir F 18 PET scan at Visit 20 of Study AZES. Florbetapir F 18 amyloid PET will be used to evaluate changes in amyloid binding from baseline of Study AZES to the end of ~~treatment.~~Year 1 of Study AZFD (Visit 11). See Schedule of Activities (Section 2). The number of florbetapir F 18 PET scans performed at Visit 11 may by limited at Sponsor discretion.

…

10. Statistical Considerations

10.1. Sample Size Determination

…

Study AZFD integrated with Study AZES forms a Delayed Start study (Study AZES-FD). Using the three stage hypothesis testing approach to delayed-start analysis as outlined in Liu-Seifert and colleagues (2015) and assuming a 5% ED rate in the first 6 months of Study AZFD and 10% ED rate in the ~~entire~~ first 12 months of Study AZFD, this sample size will provide approximately 81% power for the noninferiority test (i.e., 3rd hypothesis) for each dose when all patients have

the opportunity to complete the 6 month time point at a one-sided alpha level of 0.1. At the 12 month time point of Study AZFD, this sample size will provide approximately 66% power for the noninferiority test.

These powering results are based on solanezumab Delayed-Start results of mild dementia, ApoE4 carriers (Studies LZAM, LZAN, and LZAO). 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. The 1540 patients estimated to complete Study AZES corresponds to an assumed ED rate of 30% from the original sample size of 2202. Extending to Study AZES-FD, the assumed ED rate until the 6 month time point of Study AZFD is 35%; until the end of the three years of Study AZES-FD, the assumed ED rate is 40%. We assume an approximate 10% annual dropout over the course of Study AZFD. These ED assumptions were used to adjust the randomized sample sizes using the following formula:

…

10.3.1. General Statistical Considerations

…

~~Unless otherwise noted, all pairwise tests of treatment effects will be conducted at a 2-sided alpha level of 0.025; 2-sided confidence intervals (CIs) will be displayed with a 97.5% CI. All tests of interactions between treatments and other factors will be conducted at an alpha level of 0.025.~~ For mixed-model repeated-measures (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.~~

…

10.3.3.1. Primary Analyses

…

In the following description, the difference between an active arm and placebo at the end of Study AZES will be denoted Δ_1; the difference between delayed start and early start at the time point of interest in Study AZFD will be denoted Δ_2. Note that Δ_1 is the effect obtained from the primary analysis of Study AZES. The primary efficacy measure will be analyzed using estimates from MMRM models, in which three specific hypotheses are tested:

Test 1. Δ_1 is statistically significantly greater than 0.

Test 2. Δ_2 is statistically significantly greater than 0.

Test 3. 90% one-sided confidence limit of Δ_2 – 50% Δ_1 is greater than 0.

…

10.3.3.2. Multiplicity Adjustments

When testing the primary endpoint and each of the key secondary endpoints, ~~the first two~~Test 1 and Test 2 ~~hypotheses~~ listed in the primary analysis section ~~above~~ (Section 10.3.3.1) will be tested at the α level specified in the Study AZES multiplicity graph~~= .025 for each dose~~ in a sequential approach.~~ The three hypotheses in the primary analyses will be tested using a gatekeeping, sequential approach:~~

~~1. Δ_1 is statistically significantly greater than 0.~~

~~2. Δ_2 is statistically significantly greater than 0.~~

~~3. 90% one-sided confidence limit of Δ_2 – 50% Δ_1 is greater than 0.~~

All other pairwise tests of treatment effects will be conducted at a 2-sided alpha level of 0.025; 2-sided confidence intervals (CIs) will be displayed with a 97.5% CI. All tests of interactions between treatments and other factors will be conducted at an alpha level of 0.025.~~ No other adjustments for multiplicity are planned.~~

…

10.3.3.3. Secondary Analyses

Similar to the primary analysis, each of the key secondary efficacy outcomes (~~i~~ADL, FAQ, MMSE, CDR-SB, and iADRS) will be assessed using the primary analysis and assessed up to 26 weeks (Visit 7). The model for each of these secondary analyses will include terms for: baseline efficacy score, treatment, visit, treatment-by-visit interaction, baseline efficacy score-by-visit interaction, disease status at baseline (MCI due to AD or mild AD dementia), APOE4 status (carrier versus non-carrier), concomitant AChEI use at baseline (yes/no), age at baseline, and country. The change from baseline (prior to the initiation of treatment in Study AZES) at each visit during Study AZES-FD (at the visits when the scale being analyzed is assessed) will be the dependent variable.

In addition, the Delayed-Start methodology will be used to analyze the ADAS-Cog_{13}, ~~i~~ADL, FAQ, MMSE, CDR-SB, and iADRS at the last scheduled visit (up to Week ~~52~~ 104 [Visit ~~11~~15] of Study AZFD) to evaluate the durability of the treatment effect.

…

Appendix 1. Abbreviations and Definitions

Term	Definition
Aβ	amyloid beta peptide
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-Cog$_{13}$	13-item Alzheimer's Disease Assessment Scale-Cognition
ADCS-ADL	Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory
ADCS-iADL	Instrumental activities of the ADCS-ADL
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	amyloid-related imaging abnormality
AST	aspartate aminotransferase
AV	atrioventricular
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
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CV	cardiovascular
CYP3A4	cytochrome P450 3A4
DNA	deoxyribonucleic acid
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-5L™	A standardized instrument for use as a measure of health outcome (EuroQol Group; Rotterdam, The Netherlands)
ERB	Ethical Review Board
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)-N-methylbenzenamine)
GCP	good clinical practice
GMP	Good Manufacturing Practice
HSCRF	Hepatic Safety Case Report Form
iADRS	integrated Alzheimer's Disease Rating Scale
IB	Investigator's Brochure
ICF	informed consent form
ICH	International ~~Conference on~~Council for 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	intent~~ion~~ 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)

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
MACE	major adverse CV event
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
QTcF	QT interval adjusted for heart rate using the Fridericia formula
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBC	red blood cells
RNA	ribonucleic acid
RUD-Lite	Resource Utilization in Dementia-Lite
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.
SHFU	Self-Harm Follow-Up
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin level
ULN	upper limit of normal

VAS	visual analog scale
vMRI	volumetric magnetic resonance imaging
WBC	white blood cells

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Variables

Hematology(blood)	**Clinical Chemistry (serum)**
Hematocrit	Alanine aminotransferase (ALT)
Hemoglobin	Albumin
Leukocytes (WBC) count	Alkaline phosphatase
Absolute leukocyte differential count (neutrophils, basophils, monocytes, eosinophils and lymphocytes)	Aspartate aminotransferase (AST)
Platelet count	Bilirubin, total
	Blood urea nitrogen (BUN)
	Calcium, total
Electrolytes (serum)	C-reactive protein
Bicarbonate	Creatine kinase (CK)
Chloride	Creatinine
Phosphate	Glucose (random)
Potassium	
Sodium	**Endocrinology**
	Thyroid-stimulating hormone[a]
Urinalysis	Total thyroxine[a]
Blood	
Color	**Other**
Glucose	Hemoglobin A1c (HbA1c)[a]
Ketones	
Leukocyte esterase	
pH	
Protein	
Specific gravity	

Abbreviation: WBC = white blood cells.

[a] At Visit 11, and Visit 15 or ED only.

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Appendix 3. Study Governance Considerations

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~~ Council ~~on~~ for Harmonisation (ICH) guidelines and other applicable laws and regulations.

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