Statistical Analysis Plan I8D-MC-AZFD (Version 3)

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: 20-Aug-2018

1. Statistical Analysis Plan: 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)

LY3314814

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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Statistical Analysis Plan version 3 approved by Lilly on date provided below.

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3. Revision History

SAP Version 1 was approved prior to the first visit of the open-label study phase. The approval date was January 26, 2017. SAP Version 2 was approved prior to first iDMC release on September 20, 2017.

SAP Version 3 was approved in July 2018. See the title page for the exact approval date. Changes from version 2 to version 3 are:

- Changed various references of the study duration from 52 weeks to 104 weeks.
- Edited the objectives to align with protocol AZFD(a).
- Replaced study graph to align with graph in protocol AZFD(a).
- Aligned sample size section to align with protocol AZFD(a).
- Adjusted analyses from summarizing delayed start hypotheses to summarizing safety and efficacy data during AZFD exposure.
- Changed adjustments to multiplicity to align with protocol AZFD(a).
- Added details on imputing missing FAQ and RBANS total scores.
- Added details for pooling patients' country if the number of patients from a country is small.
- Clarified controlling alpha in multiple comparisons.
- Clarified the analysis populations.
- Dropped Kaplan-Meier analyses from disposition.
- Dropped treatment compliance summary.
- Added details to concomitant medications section.
- Changed primary efficacy analyses.
- Changed secondary efficacy analyses from delayed start analyses to MMRM analyses.
- Changed other secondary efficacy analyses from delayed start analyses to MMRM analyses.
- Changed biomarker analyses from MMRM to ANCOVA models of annualized change.
- Changed vMRI analyses from MMRM to ANCOVA models of annualized change.
- Changed efficacy scales included in the subgroup analyses to only include ADAS-Cog13 and ADCS-ADL.
- Updated the adverse event definition of treatment-emergent adverse events.

- Dropped second set of analyses of adverse events that only reports events occurring in AZFD.
- Added PCS lab summaries.
- Changed categorical analysis of weight gain or loss from 4% to 7%.
- Dropped analysis of BMI categories for patients changing more than 7%.
- Replaced CSSRS analyses originally based on studies where no/few suicidal ideations/behaviors are expected to analyses where suicidal ideations/behaviors are anticipated.
- Added description of process to handle eye exam data when patient can only count fingers.
- Added section for protocol violations.
- Added safety follow-up section.
- Corrected various typographical and formatting errors.

4. Study Objectives

4.1. Primary Objective

The primary analysis of study AZES-FD is to evaluate disease modification as outlined in Liu-Seifert (2015b). 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 with ADAS-Cog13 as the measure under investigation.

4.2. Secondary Objectives

- 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 with the American Community Survey-instrumental Activities of Daily Living (ACS--ADL), Functional Activities Questionnaire (FAQ), integrated Alzheimer's Disease Rating Scale (iADRS), Clinical Dementia Rating – Sum of Boxes (CDR-SB) and the Mini-Mental State Examination (MMSE) as the measures under investigation.
- The delayed start analyses as outlined above will also be examined through Week 104 (Visit 15) for cognitive and functional outcomes: Alzheimer's Disease Assessment Scale-13 (ADAS-Cog13), ACS--ADL, FAQ, iADRS, CDR-SB, and MMSE.
- Collect information in order to further characterize the safety and tolerability of LY3314814 in patients with early Alzheimer's disease (AD) dementia (at the time of entry into Study AZES).

5. Design and Sample Size

5.1. Summary of Study 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 depends 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 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 of the protocol. After the study was stopped for futility, all ongoing patients were asked to come in for a futility-based discontinuation visit. Patients at this visit followed the schedule of events for an early discontinuation visit.

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 AZFD.5.1 illustrates the study design.

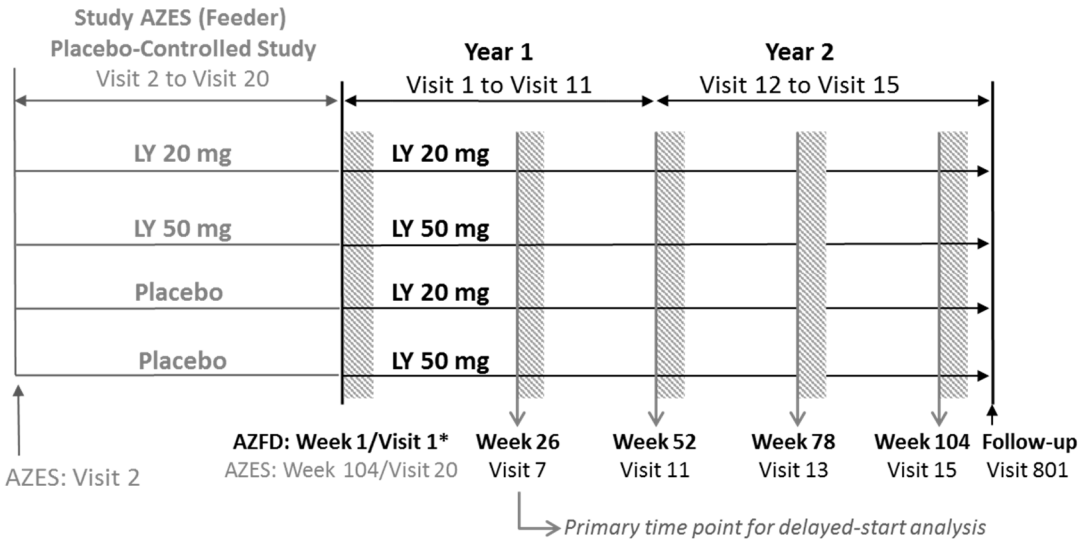

Figure AZFD.5.1. Illustration of study design for Clinical Protocol I8D-MC-AZFD.

Abbreviations: 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: Grey 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.

5.2. Determination of Sample Size

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 (hereafter referred to as Study AZES-FD). Using the three stage hypothesis testing approach to delayed start analysis as outlined in Liu-Siefert and colleagues (2015b) controlling the overall study-wide error rate at 0.05, and assuming a 5% early discontinuation rate in the first 6 months of Study AZFD and 10% early discontinuation rate in the first 12 months of Study AZFD, this sample size will provide approximately 81% power for each dose when all patients have the opportunity to complete the 6 month time point at an alpha level of 0.1. At the 12 month time point of the Delayed-Start period, this sample size will provide approximately 66% power.

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 EDC assumptions were used to adjust the randomized sample sizes using the following formula:

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

The effective sample size assumes that EDC patients will contribute half the information that completing patients contribute. The effective sample sizes for the 6 month power calculation were 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 (2015b), sig.level was set equal to 0.1 and alternative was set equal to "greater".

5.3. Method of Assignment to Treatment

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 status at baseline (MCI due to AD or mild AD dementia), the randomization will be stratified by disease status at baseline (MCI due to AD or mild AD dementia)at the time of randomization into Study AZES.

6. A Priori Statistical Methods

6.1. General Considerations

Study AZES was deemed to be futile and stopped on June 12, 2018. Because of this futility, the original primary analysis of evaluating disease modification of LY3314814 by summarizing both efficacy and safety across the placebo-controlled (study AZES) study period and delayed-start (study AZFD) study period became moot. Analyses of study AZFD described in this statistical analysis plan will summarize safety and efficacy data during patient exposure to study drug in study AZFD.

All analyses will follow the intention-to-treat (ITT) principle unless otherwise specified. An ITT analysis is an analysis of data by the groups to which subjects are assigned by random allocation, even if the subject does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. The treatment groups, reflecting the randomized treatments from the feeder study AZES, are 20 mg LY3314814, 50 mg LY3314814, placebo / 20 mg LY3314814, and placebo / 50 mg LY3314814 which will be referred to in short form as 20mg, 50mg, PL/20 and PL/50 herein. Where the ITT principle applies to random allocation, this refers to the randomization to the three treatment groups in AZES followed by the second randomization of the placebo group to one of the two LY3314814 groups in AZFD forming the four final randomized sequences (i.e., treatment groups) in the analyses.

Baseline is defined as the latest measurement taken prior to first dose of AZFD study medication. When change from baseline is assessed, subjects will only contribute to the analysis if both a baseline and a post-baseline measurement are available. Endpoint is the last non-missing post-baseline measurement in AZFD within the time period for the given analysis.

As the study was stopped for futility, the planned statistical tests lose their scientific validity and multiplicity is no longer a concern. All reported p-values will not be adjusted for multiplicity. No test will be interpreted as statistically significant, and tests resulting with low p-values will only be considered as potential results of interest. No between treatment p-values will be reported because (1) all patients receive active treatment in study AZFD, and (2) previous treatments in study AZES were randomized at AZES baseline and do not guarantee patients entering study AZFD are without selection bias. Data summaries will include a total column and columns describing the treatments received in study AZES and AZFD: 20mg, 50mg, PL/20 and PL/50.

For mixed-effect model for 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.

6.1.1. Adjustments for Covariates

The repeated measures models will include the fixed effects for baseline ADAS-Cog13, , visit, baseline ADAS-Cog13 score-by-visit interaction, disease status at baseline (MCI due to AD or mild AD), apolipoprotein 4 (APOE4) status (carrier versus non-carrier), concomitant Acetylcholinesterase Inhibitor (AChEI) use at baseline (yes/no), age at baseline, and country. The categorical factors of the model are visit, disease status at baseline (MCI due to AD or mild AD), APOE4 status (carrier versus non-carrier), concomitant AChEI use at baseline (yes/no), and country. The continuous covariates of the model are baseline ADAS-Cog13and age at baseline.

When an analysis of covariance (ANCOVA) model is used to analyze a continuous efficacy or safety variable, the model will contain the main effects of disease status at baseline (MCI due to AD or mild AD dementia), APOE4 status, and the appropriate baseline value included as a covariate.

6.1.2. Handling Missing Data from Subject Dropouts

A likelihood-based MMRM 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.

6.1.3. Handling Missing Items in Calculating Totals

All total and subscale scores for safety, efficacy, and health outcomes measures will be derived from individual items. If any of the individual items 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 items) 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 0-5 (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 as follows. 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 techniques will be applied to the Functional Activities Questionnaire (FAQ). if <30% of the items are missing, the total score will be imputed as follows. 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 FAQ at that visit will be considered missing.

The same imputation technique will be applied to the Clinical Dementia Rating-Sum of Boxes (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 the RBANS, if <30% of the sub-items are missing (ie, no more than 3 of the 12 sub-items), the item score will be imputed. For the missing subtest, the scaled score from the other subtest within that index will be used to impute the missing scaled score, which is then converted to a raw score. If List Recognition is missing, the scaled score mean for List Recall, Story Recall, and Figure Recall should be used to impute the missing value. If two sub items are missing within the same index and/or if >30% of the sub-items are missing, the total score for the RBANS 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.

6.1.4. Multicenter Studies

This study will be conducted by multiple investigators at multiple sites internationally. Country is a covariate of the primary and many of the secondary efficacy analyses. In the event that any country has an insufficient number of patients (defined as less than 20), the data from these countries will be pooled with the closest geographical country. A listing was presented in the AZES study including country, investigator site with address, number of patients enrolled (randomized) by each site and unique patient identifications (IDs).

The actual investigative site numbers will be included in the listings.

6.1.5. Multiple Comparisons/Multiplicity

As the study was stopped for futility, multiplicity is no longer a concern. All reported p-values will not be adjusted for multiplicity. No between treatment p-values will be reported because (1) all patients receive active treatment in study AZFD, and (2) previous treatments in study AZES

were randomized at AZES baseline and do not guarantee patients entering study AZFD are without selection bias.

6.1.6. Analysis Populations

The AZFD evaluable efficacy dataset will group patients according to randomized treatment assignment, even if the patient does not take the assigned treatment, does not receive the correct treatment, switches to a different treatment group if the assigned treatment group is dropped at an interim analysis, or otherwise does not follow the protocol. All patients who received at least 1 dose of AZFD study treatment will be included in the AZFD safety analysis dataset.

6.2. Patient Disposition

Patient disposition summarizes the reasons for patient discontinuation from study AZFD. The percentage of patients discontinuing from study in each treatment group will be summarized for the overall percentage and for each specific reason. Patients discontinuing treatment due to the sponsor's decision to end the phase 3 program, following the futility analysis, will have "sponsor decision" as reason for discontinuation.

6.3. Patient Characteristics

Baseline characteristics (captured at Visit 1 of Study AZES) will be summarized for the AZFD randomized population. Summaries will include descriptive statistics for continuous and categorical measures. Patient characteristics to be presented include:

- disease status at baseline (MCI due to AD or mild AD dementia)
- age
- age group: 55 to 64, 65 to 74, and 75 to 85
- gender
- race
- ethnicity
- height
- body weight
- body mass index (BMI) (weight (kg) / [height (m)]^2)
- region
- tobacco use
- alcohol use
- years of education
- work status
- method of amyloid positivity determination (PET, Cerebrospinal Fluid [CSF], historical PET)
- APOE4 carrier status (carrier [ε2/ε4, ε3/ε4, ε4/ε4], noncarrier [ε3/ε3, ε2/ε2, ε3/ε2])
- APOE4 genotype (ε2/ε4, ε3/ε4, ε4/ε4, no ε4)
- having 1 or more first degree relatives with AD
- AChEI and/or memantine use at baseline

- Baseline severity of impairment as measured by ADAS-Cog_{13}, ADAS-Cog_{11}, ADCS-ADL total score and instrumental (ADCS-iADL) and basic subscores (ADCS-bADL), CDR Sum of Boxes, MMSE, Letter and Category Fluency tests, Symbol Coding test, Neuropsychiatric Inventory (NPI), Resource Utilization in Dementia (RUD-Lite), EQ-5D Proxy, Quality of Life in Alzheimer's Disease (QoL-AD), and FAQ and RBANS.

Baseline characteristics will also be listed.

6.4. Concomitant Therapy

Concomitant medications for AZFD are defined as those being taken on or after the day of the first administration of study drug in study AZFD. Summaries of concomitant medications will be presented as frequencies and percentages. 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. Medications will be coded using the World Health Organization (WHO) drug dictionary. A summary table will also be provided for concomitant AChEI/memantine medications. Concomitant medications will be listed.

6.5. Study Partners

The protocol states every effort should be made to keep the same study partner through the duration of this trial. However, changes may be unavoidable. The percentage of patients with the same study partner will be summarized. Additionally, study partner changes will be categorized (0 changes, 1 change, and more than 1 change) and summarized.

6.6. Efficacy Analyses

6.6.1. Primary Outcome and Methodology

Study AZES was deemed to be futile and stopped on June 12, 2018. Because of this futility, the original primary analysis of AZES-FD to test the delayed-start hypothesis to evaluate disease modification by LY3314814 assessed by ADAS-Cog_{13} was moot. The primary analysis of Study AZES-FD is to summarize the ADAS-Cog_{13} change from AZES baseline across the AZES-FD visits via MMRM . The change from baseline (prior to the initiation of treatment in Study AZES) at each visit during Study AZES-FD when ADAS-Cog_{13} is assessed will be the dependent variable.

The model for the fixed effects will include terms for: baseline ADAS-Cog_{13}, visit, 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. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the following tests will be used in sequence: heterogeneous Toeplitz covariance structure, heterogeneous autoregressive covariance structure, heterogeneous compound symmetry covariance structure, and compound

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

6.7. Secondary Efficacy Analyses

6.7.1. Secondary Analyses

The efficacy measures that are aligned with the secondary objectives (ADCS-ADL, FAQ, MMSE, CDR-SB, and iADRS) will be analyzed using the MMRM analysis described in Section 6.6.1. The model for each of these secondary analyses will include terms for: baseline efficacy score, visit, 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.

6.7.2. Health Outcomes/Quality-of-Life Analyses

Analyses of the EQ-5D combined component scores and of the RUD-Lite will follow the same methods as outlined in Section 6.7.1. These measures are assessed at week 19 instead of week 26 and week 45 instead of week 52 so the model for these results will be adjusted accordingly.

6.8. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Annualized change in bioanalytical biomarkers for each patient will be calculated using the change in CSF at the last post-baseline visit. The annualized change will be analyzed with an ANCOVA. The ANCOVA model will include the following independent variables: baseline value, age at baseline, and disease status at baseline (MCI due to AD or mild AD).

6.8.1. Analysis of Plasma Aβ

The plasma Aβ analytes (including assayed plasma Aβ1-40 and Aβ1-42) will be analyzed using the ANCOVA methods described in Section 6.8.

6.8.2. Analyses of Amyloid PET Data

The composite summary standard uptake value ratio (SUVr) of AV-45 (florbetapir F 18 PET scan) normalized (based on whole cerebellum and based on atlas-based white matter) will be analyzed using the ANCOVA methods described in Section 6.8. The change from baseline score at each scheduled postbaseline visit (according to the Study Schedule) during the treatment period will be analyzed.

6.8.3. Analyses of CSF Biomarker Data

The CSF biomarkers (including total CSF Aβ1-40, total CSF Aβ1-42, CSF total tau, and CSF p-tau from lumbar puncture) will be analyzed using the ANCOVA methods described in Section 6.8. The change from baseline score at each scheduled postbaseline visit (according to the Study Schedule) during the treatment period will be analyzed.

6.8.4. Analyses of FDG PET Data

Two composite summary standard uptake value ratios (SUVr) of FDG PET normalized to the pons + vermis will be assessed: (1) Composite Meta and (2) Composite Meta Automated Anatomical Labeling atlas (AAL). The SUVRs will be analyzed using the ANCOVA methods described in Section 6.8. The change from baseline score at each scheduled postbaseline visit (according to the Study Schedule) during the treatment period will be analyzed.

6.8.5. Analyses of Tau PET Data

The composite summary standard uptake value ratio (SUVr) of Tau PET computed from the MUBADA region with the bimodal white matter serving as the reference region normalized to bimodal white matter will be analyzed using the ANCOVA methods described in Section 6.8. The change from baseline score at each scheduled postbaseline visit (according to the Study Schedule) during the treatment period will be analyzed.

6.9. Analyses of vMRI Data

Analyses of the following volumetric MRI (vMRI) parameters will be conducted (right + left for all but whole brain volume and ventricular volume):

- Hippocampal volume (mm^3)
- Entorhinal cortex (mm^3)
- Inferior parietal lobe (mm^3)
- Isthmus cingulate (mm^3)
- Lateral parietal lobe (mm^3)
- Medial temporal lobe (mm^3)
- Precuneus (mm^3)
- Prefrontal lobe (mm^3)
- Superior temporal lobe (mm^3)
- Atrophy of Total whole brain volume (cm^3)
- Enlargement of Ventricular volume (cm^3)

All of the above volumes are corrected for intracranial volume. Annualized change in volumetric magnetic resonance imaging (vMRI) for each patient will be calculated using the change in vMRI at the last post-baseline visit. The annualized change will be analyzed with an ANCOVA model on the full efficacy dataset. The ANCOVA model will include fixed, categorical effects of disease status at baseline (MCI due to AD or mild AD) as well as the continuous effects of baseline vMRI value, and age at baseline.

6.10. Safety Analyses

6.10.1. Extent of Exposure

Days of exposure will be calculated for each patient for the AZFD period as (date of last dose – date of first dose of the AZFD period +1). Summary statistics will be provided for the total number of days and patient-years of exposure. Study drug treatment assignment will be listed.

6.10.2. Adverse Events

Treatment-emergent adverse events (TEAEs) will be defined as events that first occurred or worsened after the randomization date (Visit 1 date). The treatment-emergent period ends on the last day of treatment plus 5 days (these 5 days constitute at least 5 half-lives of lanabecestat). Events occurring within the study but during a period of treatment interruption will only be treated as treatment-emergent if they occur within 5 days of the last dose prior to the treatment interruption. Should there be insufficient data for AE start date, stop date, and time to make this comparison, the AE will be considered treatment-emergent.

The MedDRA lower-level term (LLT) will be used in the treatment-emergent computation. The maximum severity for each lower-level term (LLT) during the baseline period will be used as baseline.

Summaries of AEs by decreasing frequency of preferred term within system organ class will be provided for the following:

- TEAEs
- TEAEs by maximum severity
- TEAEs occurring in greater than or equal to 2% of patients by preferred term
- Serious adverse events (SAEs)
- AEs reported as reason for study treatment discontinuation

These summaries will include number and percentages of patients with TEAEs. For TEAEs by maximum severity, Severity =”Severe” and “More Severe” will be combined into “Severe” category.

6.10.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

An overview of AEs, including the number and percentage of patients who died, suffered SAEs, discontinued due to AEs and who suffered TEAEs, will be provided.

In addition, the proportion of patients within specific clusters of TEAEs will be summarized. Clusters will be created from MedDRA High Level Group Terms (Table AZFD.6.1) and MedDRA standardized MedDRA Queries (SMQs).

Table AZFD.6.1. Adverse Events of Special Interest

AE Groups of Interest (Clusters)	MedDRA HLGT
Nervous System Disorders	Neuromuscular Disorders HLGT Demyelination SMQ Peripheral Neuropathy SMQ
Eye Disorders	Retinal disorders SMQ
Skin Disorders	Sub-group A: Epidermal and Dermal Conditions HLGT (excluding sub-group B terms) Sub-group B (Hypopigmentation-related events): Hypopigmentation disorders HLT Pigmentation changes, NEC HLT Preferred terms: 'hair depigmented', 'eyelash discolouration', 'iris hypopigmentation', 'eye colour change', 'lip colour altered', 'lip discolouration', 'hair colour changes', 'achromotrichia aquired', 'poliosis'
Liver Disorders	Drug related hepatic disorders - comprehensive search SMQ
Cardiovascular-type events – Arrhythmic	Arrhythmia related investigations, signs and symptoms SMQ Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) SMQ TdP/QT prolongation SMQ
Cardiovascular-type events – Ischemic	Ischaemic heart disease SMQ
Cardiovascular-type events – Stroke	Central nervous system vascular disorders SMQ
Cardiovascular-type events – including orthostatic hypotension	Decreased and Nonspecific Blood Pressure Disorders and Shock HLGT

Abbreviations: SMQ = standardized MedDRA Query, NEC = Not Elsewhere Classified, HLGT = High Level Group Term; TdP/QT = Torsades de pointes /QT interval.

6.10.4. Clinical Laboratory Evaluation

Laboratory measurements will be analyzed using continuous data (change from baseline) and categorical or ordinal data (proportion of treatment-emergent abnormalities) for AZFD. If there are multiple records of laboratory measurements at a baseline or postbaseline visit, the last record will be used. Summaries and analyses of continuous data (change from baseline) will be performed using both conventional and International System of Units (SI units).

Change from baseline to post-baseline visit at which laboratory measurements are taken will be analyzed using an MMRM model. For each lab analyte, the rank-transformation will be applied to the change from baseline for all patients and all visits prior to analysis. Similarly, an independent rank-transformation will be applied to the baseline values prior to analysis. The model for the fixed effects will include terms for the following independent effects: ranked baseline value, visit, and disease status at baseline (MCI due to AD or mild AD). This analysis will be done separately for each laboratory analyte.

The proportion of patients with treatment-emergent high or treatment-emergent low or treatment-emergent abnormal laboratory values at (1) anytime and (2) each post-baseline visit will be summarized. Treatment-emergent high or low laboratory abnormality will be based on SI unit. For each laboratory analyte, only patients who were low or normal at baseline and have at least one post-baseline measurement will be included in the denominator when computing the proportion of patients with treatment-emergent high results. Similarly, only patients who were high or normal at baseline and have at least one post-baseline measurement will be included in the denominator when computing the proportion of patients with treatment-emergent low results. In addition, the proportion of patients who have normal baselines with a change to abnormal high or abnormal low values at any post-baseline visit will be summarized. For urinalysis parameters, baseline to post-baseline shifts will be summarized at each visit.

A second categorical analysis will be conducted on laboratory analytes. This analysis is considered a PCS analysis and will use limits typically wider than the first categorical analysis. Abnormal criteria for these treatment-emergent PCS changes are presented in Appendix 3.

For urinalysis parameters, baseline to post-baseline shifts will be summarized at each visit.

The proportion of patients with treatment-emergent clinically significant changes from a low value or normal value at all baseline at any time in ALT and total bilirubin will be summarized by treatment group. Clinically significant changes of interest at any time are: alanine transaminase (ALT) ≥ 3 x upper limit of normal (ULN) and total bilirubin ≥ 2 x ULN, aspartat aminotransferase (AST) ≥ 3 x ULN, ALT ≥ 5 x ULN, ALT ≥ 10 x ULN, and total bilirubin ≥ 2 x ULN. Additionally, Hy's Law analysis will be summarized with regard to the proportion of patients with (ALT ≥ 3 x ULN or AST ≥ 3 x ULN) and total bilirubin ≥ 2 x ULN at any time. When criteria are met for hepatic evaluation and completion of the hepatic safety case report form (CRF), investigators are required to answer a list of questions pertaining to the patient's history, relevant pre-existing medical conditions, and other possible causes of liver injury. A listing of the information collected on the hepatic-safety CRF will be generated.

6.10.5. Vital Signs and Other Physical Findings

Vital sign measurements and weight will be analyzed using continuous data (change from baseline) and categorical data (proportion of potentially clinically significant changes) for AZFD.

If there are multiple records of vital sign or weight measurements at baseline or postbaseline visits, the last record will be used. Summary statistics will be presented for observed values at baseline and for change from baseline results at each scheduled postbaseline visit. Systolic and diastolic blood pressure and pulse (collected in sitting position), orthostatic diastolic and systolic blood pressures and orthostatic pulse (measurement after 5 minutes in the supine position minus that after 2 and 5 minutes in the standing position), temperature, and weight by treatment group for all patients in the safety population will be summarized.

With the large number of visits at which vital signs are scheduled to be measured, the MMRM model is not suitable for the change from baseline comparison of treatment groups. Change from

baseline to each post-baseline visit at which vital signs are taken will be assessed using an ANCOVA model with baseline value and age as covariates in the model. This analysis will be done separately for each vital sign parameter and weight.

The incidence of treatment-emergent abnormal high or low vital signs and weight will be presented by treatment group and visit. Treatment-emergent vital sign evaluations are those collected after the initiation of study medication. Abnormal criteria for post-baseline vital signs and weight are presented in Appendix 4. Any vital sign or weight meeting the criteria will be considered abnormal. Summaries of the proportion of patients with treatment-emergent abnormal high or low vital signs and weight will be assessed between treatment groups using Fisher's exact test at (1) any time and (2) each post-baseline visit. For each vital sign at each post-baseline visit, only patients who had a baseline result and had a nonmissing result at that post-baseline visit will be included in the denominator when computing the proportion of patients with treatment-emergent high, low, or abnormal values.

Summary and analyses of change from baseline in weight will be provided. The proportion of patients with a weight gain or loss of greater than or equal to 7 percent of baseline body weight will be summarized at each visit and at any time.

A listing of treatment-emergent abnormal vital signs and weight will also be presented.

6.10.6. Electrocardiograms

Electrocardiograms (ECG) measurements will be analyzed using continuous data (change from baseline) and categorical data (proportion of treatment-emergent abnormalities) for AZFD.

The ECG measurements are derived from three 10 second readings taken every 30 seconds. These 3 readings are to be averaged prior to analysis. Additionally, whenever ECG is measured in triplicate, the average of these readings will be used in the analysis. If there are multiple records after averaging ECG triplicates within a visit, the last record of averages will be used. The analysis will be done for the following ECG measurements: heart rate, PR, QT, QTc, and RR intervals and QRS duration. All analyses of QTc will be carried out using the Fridericia correction (QTcF) method. These summaries will include data from each visit at which ECG measurements are taken. Change from baseline to each post-baseline visit at which ECG measurements are taken will be assessed using an MMRM model. The model for the fixed effects will include terms for the following independent effects: baseline ECG score, visit, and age at baseline. This analysis will be done separately for each ECG parameter.

Treatment-emergent high ECG parameters (heart rate, PR interval, QRS duration, QT and QTcF intervals) are the values which are low or normal at all baseline visits and fall into the high abnormal categories post-baseline. Similarly, treatment-emergent low ECG parameters (heart rate, PR interval, QRS duration) are the values which are high or normal at all baseline visits and fall into the low abnormal categories above. In addition, treatment differences in the proportion of patients who have normal baselines with a change to abnormal high or abnormal low values at any post-baseline visits will be summarized. Incidence of treatment-emergent abnormal ECGs will be summarized at (1) any time and (2) each post-baseline visit. For analyses of treatment-

emergent abnormal ECGs, baseline will be considered as all visits before the initiation of drug dose in Study AZES. Abnormal ECG criteria and criteria for abnormal QTcF prolongation are presented in Appendix 5.

6.10.7. Analyses of MRI Data

The MRI analyses will apply to AZFD. Frequencies and percentages of the following amyloid-related imaging abnormality – edema (ARIA-E, also known as vasogenic edema) and ARIA – hemorrhage (ARIA-H, also known as microhemorrhage) parameters will be summarized:

- ARIA-E:
  - Severity (mild, moderate, severe, or no presence)
  - Status compared to the previous MRI(s) (questionable, increased, unchanged, decreased, no longer present)
- ARIA-H:
  - Number of ARIA-H (1, 2 to 5, 6 to 10, >10, or no presence),
  - Baseline to endpoint changes (increase in size of pre-existing ARIA-H, increase in number of ARIA-H, no change, partial resolution, or complete resolution)

To evaluate white matter changes over time, a shift table will be created from the following categories:

- 0 = No lesions
- 1 = Focal lesions
- 2 = Beginning confluence of lesions
- 3 = Diffuse involvement of entire region

A listing of MRI data will also be presented.

6.10.8. Additional Safety Concerns

6.10.8.1. Columbia Suicide Severity Rating Scale

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent occurring during treatment, based on the Columbia-Suicide Severity Rating Scale (C-SSRS), will be summarized by treatment. In particular, for each of the following events, the number and percent of patients with the event will be enumerated by treatment: completed suicide, nonfatal suicide attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, active suicidal ideation with specific plan and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods (no plan) without intent to act, nonspecific active suicidal thoughts, wish to be dead, and self-injurious behavior without suicidal intent. Although not suicide-related, the number and percent of patients with non-suicidal self-injurious behavior occurring during the treatment period will also be summarized by treatment.

In addition, the number and percent of patients who experienced at least one of various composite measures during treatment will be presented and compared. These include suicidal behavior (completed suicide, non-fatal suicidal attempts, interrupted attempts, aborted attempts, and preparatory acts or behavior), suicidal ideation [active suicidal ideation with specific plan

and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods (no plan) without intent to act, non-specific active suicidal thoughts, and wish to be dead], and suicidal ideation or behavior.

The number and percent of patients who experienced at least one of various comparative measures during treatment will be presented and compared. These include treatment-emergent serious suicidal ideation compared to recent history, emergence of serious suicidal ideation compared to recent history, improvement in suicidal ideation at endpoint compared to baseline, and emergence of suicidal behavior compared to all prior history (including AZES and prior to AZES).

Specifically, the following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale to facilitate the definitions of the composite and comparative endpoints, and to enable clarity in the presentation of the results.

Category 1 – Wish to be Dead
Category 2 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5 – Active Suicidal Ideation with Specific Plan and Intent
Category 6 – Preparatory Acts or Behavior
Category 7 – Aborted Attempt
Category 8 – Interrupted Attempt
Category 9 – Actual Attempt (non-fatal)
Category 10 – Completed Suicide

Self-injurious behavior without suicidal intent is also a C-SSRS outcome (although not suicide-related) and has a binary response (yes/no).

Composite endpoints based on the above categories are defined below.

- Suicidal ideation: A "yes" answer at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS.
- Suicidal behavior: A "yes" answer at any time during treatment to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS.
- Suicidal ideation or behavior: A "yes" answer at any time during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

The following outcome is a numerical score derived from the C-SSRS categories. The score is created at each assessment for each patient and is used for determining treatment emergence.

- Suicidal Ideation Score: The maximum suicidal ideation category (1-5 on the C-SSRS) present at the assessment. Assign a score of 0 if no ideation is present.

Comparative endpoints of interest are defined below. "Treatment emergence" is used for outcomes that include events that first emerge or worsen. "Emergence" is used for outcomes that include events that first emerge.

- Treatment-emergent suicidal ideation compared to recent history (last visit of AZES):

An increase in the maximum suicidal ideation score during treatment (Visits Y1-Y2) from the maximum suicidal ideation category during the screening and lead-in periods (C-SSRS scales taken at Visits X1-X2). Recent history excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale.

- Treatment-emergent serious suicidal ideation compared to recent history (last visit of AZES): An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment (Visits Y1-Y2) from not having serious suicidal ideation (scores of 0-3) during the screening and lead-in periods (C-SSRS scales taken at Visits X1-X2). Recent history excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale.
- Emergence of serious suicidal ideation compared to recent history (last visit of AZES): An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment (Visits Y1-Y2) from no suicidal ideation (scores of 0) during the screening and lead-in periods (C-SSRS scales taken at Visits X1-X2). Recent history excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale.
- Improvement in suicidal ideation at endpoint compared to baseline (AZES visit 20): A decrease in suicidal ideation score at endpoint (the last measurement during treatment; Visits Y1-Y2) from the baseline measurement (the measurement taken just prior to treatment; (Visit X2). This analysis should only be performed for a non-lifetime baseline measurement (i.e., having improvement from the worse event over a lifetime is not clinically meaningful). A specific point in time can be used instead of endpoint.
- Emergence of suicidal behavior compared to all prior history (including AZES and prior to AZES):

  The occurrence of suicidal behavior (Categories 6-10) during treatment (Visits Y1-Y2) from not having suicidal behavior (Categories 6-10) prior to treatment (Visits X1-X2). Prior to treatment includes "lifetime" and/or "screening" scores from the Baseline C-SSRS scale, Screening C-SSRS scale, or Baseline/Screening C-SSRS scale, and any "Since Last Visit" from the Since Last Visit C-SSRS scales taken prior to treatment.

Patients who discontinued from the study with no postbaseline C-SSRS value will be considered unevaluable for analyses of suicide-related events. Only evaluable patients will be considered in the analyses.

6.10.8.2. Skin Examination

Skin color will be reported at baseline using Fitzpatrick Scale Rating. The frequencies of the Fitzpatrick Scale Rating (I, II, III, IV, V, and VI) will be displayed by treatment group. Frequency tables and summary statistics for continuous parameters will be given by treatment group.

Any 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 (sPGA) will be used to determine the patient's overall hypopigmentation severity at a given timepoint using a visual analog scale (VAS) ranging from 0

to 100. In addition, patients noted to have evidence of hypopigmentation will be asked to record how bothersome they find the hypopigmentation to be on a VAS ranging from 0 to 100. Additionally, the percentage of patients with emergence of greater than expected hair hypopigmentation will be summarized for patients 'no' at baseline if question is available on worksheet.

In order to display any changes/deteriorations during treatment, the following will be reported: number of patients for whom no hypopigmentation was observed at baseline, but for whom at least once after randomization hypopigmentation was observed during the treatment period; summary statistics for the difference of maximum value during treatment minus baseline value for percentage body surface area (BSA) of hypopigmentation; shift table of baseline vs. maximum value during treatment for degree of overall lesion severity. Summary statistics for the change in overall severity (sPGA) and "how bothered is the patient" will be reported for patients with emergence of hypopigmentation, increased severity of hypopigmentation, or increased BSA during the study.

6.10.8.3. Eye Examination

Frequency tables will be produced for all time points for performance of eye examination, visual acuity examination, intraocular pressure examination, and slit lamp exam status and dilated fundus exam status (normal, abnormal – clinically not significant, and abnormal – clinically significant). Clinically significant abnormalities will be displayed together with the corresponding specifications of abnormalities in separate individual data listings.

Summary statistics will be produced for the following continuous parameters: left eye total visual acuity score, right eye total visual acuity and both eyes score (scores expressed as logMAR calculated as the negative log (base 10) of the decimal scores)), as well as left eye intraocular pressure and right eye intraocular pressure (both in mmHg). For visual acuity, "count fingers" will be given a decimal score of 0.01 and a logMAR of 2 (reference http://www.hicsoap.com/publications/ProperMethodforCalculating.pdf). "Light perception" and "no light perception" cannot be assigned decimal or LogMAR values and so are treated as missing in the mean change summary tables. Visual acuities of patients with these values at any time during the study will be provided in a separate listing.

In order to display any changes/deteriorations during treatment, the following will be reported: number of patients with potentially clinically significant changes (slit lamp examination or dilated fundus examination) documented during treatment that was not already present at baseline; summary statistics for the difference of maximum value during treatment minus baseline value for left eye total visual acuity score, right eye total visual acuity score, left eye intraocular pressure (mmHg), and right eye intraocular pressure (mmHg). Worst assessment of overall eye examination results during treatment with possible entries "unchanged", "new", "improved", and "worsened".

6.11. Protocol Violations

Listings of patients with significant protocol violations will be provided for the Randomized population. The following list of significant protocol violations will be determined from the clinical database and from the clinical/medical group:

- Informed consent violation detected as a missing date of informed consent.
- Did not have an assessment of either the ADAS-Cog at any of the visits at which the scales were scheduled to be assessed.
- Not compliant with study drug calculated as taking less than 80% or greater than 120% of study drug while the subject was expected to be on treatment.

The following list of significant protocol violations will be determined by clinical/medical group:

- Protocol violations of inclusion/exclusion criteria.
- Had a study dosing algorithm violation (such as if patients randomized to treatment A were given treatment B or patients randomized to treatment A never received the assigned study drug.)
- Unqualified raters for the ADAS-Cog.

Other protocol violations reported through the monitoring process will be reviewed by the study team and if judged to be significant, will be added to the final reported listing.

6.12. TLSR and iDMC

The reports for the trial-level safety reviews and the independent data monitoring committee will summarize categorical safety data which first occurred or worsened in study AZFD using the AZES baseline. Mean change from baseline reports will use the AZES baseline and only report changes occurring in AZFD.

6.13. Safety Follow-Up Visit

Patients who choose to withdraw from the study upon discontinuing study treatment and after completing the early discontinuation visit assessments, as appropriate, should be asked to return for a follow-up visit (Visit 801) within 4 to 6 weeks of discontinuing treatment. Adverse events, concomitant medications, vital signs, and ECGs will be collected at these visits. Separate summaries of adverse events, concomitant medications, C-SSRS, PCS vital signs and PCS ECGs will be created for the safety follow-up data from Visit 801.

6.14. Clinical Trial Registry Analyses

Analyses provided for the clinical trial registry (CTR) requirements include the following:

Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized: by treatment group, by MedDRA preferred term.

- An AE is considered 'Serious' whether or not it is a TEAE.

- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event - the number at risk can be different for different events, particularly if they are gender-specific events
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of subjects/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).

7. References

Andersen SW, Millen BA. On the practical application of mixed effects models for repeated measures to clinical trial data. *Pharm Stat*. 2013;12:7-16. doi: 10.1002/pst.1548.

Brannath W, Koenig F, Bauer P. Multiplicity and flexibility in clinical trials. *Pharm Stat*. 2007;6:205-216.

Cedarbaum JM, Jaros M, Hernandez C, Coley N, Andrieu S, Grundman M, et al. Rationale for use of the Clinical Dementia Rating Sum of Boxes as a primary outcome measure for Alzheimer's disease clinical trials. *Alzheimers Dement*. 2013;9(1 Suppl):S45-S55.

Diggle PD, Kenward MG. Informative dropout in longitudinal data analysis (with discussion). *Appl Stat*. 1994;43:49-93.

Liu-Seifert H, Andersen SW, Lipkovich I, Holdridge KC, Siemers E. A novel approach to delayed-start analyses for demonstrating disease-modifying effects in Alzheimer's disease. *PLoS ONE*. 2015;10(3):Article No: e0119632.

Lyketsos CG, Breitner JCS, Rabins PV. Evidence-based proposal for the classification of neuropsychiatric disturbance in Alzheimer's disease. *Int J Geriatr Psychiatry*. 2001a;16:1037-1042.

Lykestos CG, Sheppard JE, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JCS. Neuropsychiatric disturbance in Alzheimer's disease clusters into three groups: the Cache County study. *Int J Geriatr Psychiatry*. 2001b;16:1043-1053.

Mohs R, et al. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology*. 2001;57:481-488.

Tun S, Murman DL, Long HL, Colenda CC, von Eye, A. Predictive validity of neuropsychiatric subgroups on nursing home placement and survival in patients with Alzheimer Disease. *Am J Geriatr Psychiatry*. 2007;15(4):314-327.

8. Appendices

Appendix 1. Complete List of AV-45 Parameters

SUVr will be obtained for the regions listed below normalized to whole cerebellum and to patient-specific white matter:

- composite summary
- anterior cingulate
- frontal medial orbital
- parietal
- posterior cingulate
- precuneus
- temporal

The composite summary measure is an unweighted average of the 6 smaller regions listed.

Appendix 2. Complete List of FDG Pet Parameters

SUVr will be obtained for the regions listed below normalized to the pons, whole cortex and group of voxels with AD-preserved activity (Herholz et al. 2002).

composite summary	lateral temporal cortex left	pons
caudate left	lateral temporal cortex right	putamen right
caudate right	mean cerebellum gray matter	putamen left
cerebellar cortex left	mean whole cerebellum	rectus left
cerebellar cortex right	mesial temporal cortex left	rectus right
cerebellar white matter	mesial temporal cortex right	subcortical white matter
cingulum anterior left	lateral occipital cortex left	temporal cortex left[a]
cingulum anterior right	lateral occipital cortex right	temporal cortex right[a]
cingulum posterior left[a]	orbitofrontal cortex left	thalamus left
cingulum posterior right[a]	orbitofrontal cortex right	thalamus right
lateral frontal cortex left	lateral parietal cortex left	angular left[a]
lateral frontal cortex right	lateral parietal cortex right	angular right[a]
		whole cortex
		region with AD-preserved uptake
		precuneus left
		precuneus right

[a] Regions used in calculation of the composite summary SUVr.

Appendix 3. Potentially Clinically Significant Laboratory Values

Parameter	SI Unit	Low PCS Criteria	High PCS Criteria
Hematology (whole blood)			
Hemoglobin (male)	mml/L-Fe	<6.8266	>11.1708
Hemoglobin (female)	mml/L-Fe	<6.206	>10.5502
Hematocrit	Proportion of 1.0	<0.3	>0.50 (F); >0.55 (M)
Leukocyte (WBC Count)	10^9/L	≤2.8	≥15
Neutrophils	10^9/L	≤1.5	NA
Platelet Count	10^9/L	≤75	≥700
Chemistry (serum or plasma)			
ALT (SGPT)	U/L	NA	≥3 X ULN
AST (SGOT)	U/L	NA	≥3 X ULN
Total Bilirubin	umol/L	NA	≥1.5 ULN
BUN	mmol/L	NA	≥1.2 ULN
Creatinine Kinase (CK)	U/L	NA	≥3ULN
Sodium	mmol/L	≤125	≥155
Potassium	mmol/L	≤3.0	≥5.5
Calcium	mmol/L	≤0.7 ULN	≥1.2 ULN
Alkaline Phosphatase	U/L	NA	≥3ULN
Albumin	g/L	≤26	≥60
Chloride	mmol/L	≤85	≥120
Glucose (random)	mmol/L	≤0.3 ULN	≥1.5 ULN
Serum Creatinine	umol/L	NA	>1.5 ULN
TSH	mIU/L	below normal range	above normal range
Urinalysis			
Hb/RBCs/Blood		NA	≥ + 2
Protein/Albumin		NA	≥ + 2
Glucose		NA	≥ + 2

Abbreviations: ALT/SGPT = alanine aminotransferase/serum glutamic pyruvic; AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase; BUN = blood urea nitrogen; Hb = heart beat, PCS = potentially clinically significant; RBC = red blood cells; TSH = thyroid stimulating hormone; ULN = upper limit of normal; WBC = white blood cells.

Appendix 4. Potentially Clinically Significant Vital Signs and Weight

Potentially Clinically Significant Vital Signs and Weight

Vital Sign Parameter (Unit)	Postbaseline Low Criteria	Postbaseline High Criteria
Sitting Systolic Blood Pressure (mmHg)	Absolute value ≤90 and ≥20 decrease from baseline	Absolute value ≥160 and ≥20 increase from baseline
Sitting Diastolic Blood Pressure (mmHg)	Absolute value ≤50 and ≥10 decrease from baseline	Absolute value ≥100 and ≥10 increase from baseline
Sitting Pulse (bpm)	Absolute value <50 and ≥15 decrease from baseline	Absolute value >100 and ≥15 increase from baseline
Weight	≥7% decrease	≥7% increase
Vital Sign Parameter (Unit)	**Postbaseline Criteria for Abnormality**	
Orthostatic Systolic Blood Pressure (mmHg)	≥20 decrease in systolic blood pressure (supine to standing) (ie, supine minus standing ≥20)	
Orthostatic Diastolic Blood Pressure (mmHg)	≥10 decrease in diastolic blood pressure (supine to standing) (ie, supine minus standing ≥10)	
Orthostatic Pulse (bpm)	≤ -30 decrease (supine to standing) (ie, supine minus standing ≤ -30)	
Temperature	Absolute value ≥38.3°C and ≥1.1°C increase from baseline (Absolute value ≥101°F and ≥2°F increase from baseline)	

Abbreviations: bpm=beats per minute, NA=not applicable.

Appendix 5. Potentially Clinically Significant ECGs

Potentially Clinically Significant ECGs

Parameter	Unit	Low PCS Criteria	High PCS Criteria
QRS Interval	msec	NA	≥120
PR Interval	msec	<100	≥220
Heart Rate	bpm	<45	≥120
QTcF	msec	<320	>500
QTcF interval: change from baseline	>60 msec at any time after randomization		

Abbreviation: PCS = potentially clinically significant.

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