Janssen Research & Development *

Statistical Analysis Plan

A Randomized, Two-Period, Double-Blind Placebo-Controlled and Open-Label, Multicenter Extension Study to Determine the Long-Term Safety and Tolerability of JNJ-54861911 in Subjects in the Early Alzheimer's Disease Spectrum

Protocol 54861911ALZ2004; Phase 2

JNJ-54861911 (atabecestat)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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AMENDMENT HISTORY

ABBREVIATIONS

Aβ	amyloid β (beta)
AD	Alzheimer's disease
AE	adverse event
APP	amyloid precursor protein
BACE	β-secretase
BMI	body mass index
CDR	Clinical Dementia Rating Scale
CDR-SB	Clinical Dementia Rating Scale – Sum of Boxes
CFI	Cognitive Function Index
CI	confidence interval
CRF	case report form
CSF	cerebrospinal fluid
CSR	Clinical Study Report
CVLT-II	California Verbal Learning Test – Second Edition
ECG	Electrocardiogram
eCRF	electronic case report form
ICF	informed consent form
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
PCI	potentially clinically important
PD	Pharmacodynamic
PK	pharmacokinetic(s)
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SAE	serious adverse event
sAPP	soluble amyloid precursor protein
SAP	Statistical Analysis Plan
SD	standard deviation
TE	treatment-emergent

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the safety, pharmacodynamic (PD)/biomarker, clinical and cognitive evaluation analyses for **Periods 1 and 2**.

1.1. Trial Objectives

Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of JNJ-54861911 in subjects in the early AD spectrum that have completed a Phase 1b or Phase 2 clinical trial with JNJ-54861911 (e.g. Study 54861911ALZ2002), who are willing to continue their assigned treatment.

Secondary Objectives

The secondary objectives of this study in subjects in the early AD spectrum are:

- To assess the maintenance of JNJ-54861911 effects on markers of Aβ processing (Aβ1-37, Aβ1-38, Aβ1-40, Aβ1-42) in CSF and plasma.
- To assess the relationship of changes in CSF and plasma Aβ species (Aβ1-37, Aβ1-38, Aβ1-40, Aβ1-42) with safety.
- To assess changes in CSF p-tau, t-tau and/or additional alternate biomarkers of neurodegeneration following long term treatment with JNJ-54861911.
- To assess the plasma and CSF pharmacokinetics of JNJ-54861911 in a patient population using a population PK approach and explore its relationship with efficacy and safety parameters.
- To provide ongoing access to JNJ-54861911

Exploratory Objectives

- To explore if JNJ-54861911 will slow the rate of cognitive decline, the perceived cognitive function, and performance of everyday activities.
- To assess the annual conversion rate of subjects treated with JNJ-54861911 to the different stages/phases of the AD spectrum.
- To explore the potential relationship of markers of neurodegeneration (volumetric magnetic resonance imaging [MRI], CSF t-tau or p-tau, with cognitive decline and/or response to treatment with JNJ-54861911.

1.2. Trial Design

This is a randomized, two-period, double-blind (DB) placebo controlled and open-label (OL), multi-center, parallel-group study assessing primarily the long-term safety and tolerability of JNJ-54861911 in subjects in the early AD spectrum that have completed a Phase 1b or Phase 2 clinical study with JNJ-54861911.

Subjects who provide consent to enroll in this study and who meet the inclusion criteria, may start at Day 1 of the DB treatment phase in lieu of the end of treatment visit in 54861911ALZ2002 study. For subjects that have completed the end of treatment visit in the 54861911ALZ2002 study enrollment in this study should be completed (Day 1 of DB treatment phase) as soon as possible, but within 6 weeks, following completion of their treatment period under the parent protocol (54861911ALZ2002 study) of currently ongoing or any future Phase 1b or Phase 2 studies with JNJ-54861911.

Eligible subjects enrolled in this study will receive either JNJ-54861911 (10 mg or 25 mg q.d.) or placebo (q.d.). Subjects will continue with their current treatment regimen established in the parent JNJ-54861911 study (e.g. for 54861911ALZ2002 placebo or JNJ-54861911) for a period of 52 Weeks (12 Months) (placebo-controlled DB treatment phase).

Following the initial 52-Week (12-Month) treatment phase (DB treatment phase) in this study, subjects receiving placebo in the DB treatment phase will be randomized with equal chance to one of 2 active JNJ-54861911 dose levels (i.e., 5-mg q.d JNJ-54861911 or 25-mg q.d. JNJ-54861911) for continuous treatment in OL phase. As such during OL phase, all subjects will receive active (JNJ-54861911) treatment (open-label). In addition, subjects who were receiving 10 mg q.d. JNJ-54861911 will have their dose reduced to 5 mg q.d. in order to harmonize the dosage with that of the Phase 2b/3 program, while subjects who were receiving 25 mg q.d. will continue to receive that dosage.

1.3. Statistical Hypotheses for Trial Objectives

This is a study to collect primarily long-term safety and tolerability data. There is no formal hypothesis testing planned for this long-term study which is an extension of 54861911ALZ2002 study.

1.4. Sample Size Justification

The study is not powered according to statistical calculations. The number of subjects enrolled will depend on the number of subjects from other JNJ-54861911 studies who are willing to enroll in this extension study.

1.5. Randomization and Blinding

During the DB treatment phase, subjects will receive either JNJ-54861911 (10-mg or 25-mg q.d.) based on their current treatment/dosing regimen assigned under the parent protocol (54861911ALZ2002).

Both the investigator and subject will be blinded during Treatment Period 1 of the study.

Regarding the sponsor, when the parent study (54861911ALZ2002) is completed and its clinical database is closed, the randomization codes from the parent study will be released to the sponsor study team. Thus, the sponsor will be unblinded at that time, but the investigator and subjects will continue to be blinded to treatment during DB treatment phase. (cf. Protocol Amendment 2)

2. GENERAL ANALYSIS DEFINITIONS

Statistical analyses will be performed for all subjects receiving at least one dose of study drug in this study Period 1. This analysis summarizes double-blind treatment Period 1 and open-label Period 2. All analyses will be performed using SAS Version 9.4[1] or higher.

2.1. Analysis Phase

Period 1 start date will be the date and time of first administration of double-blind study medication. Period 1 end date will be equal to the date of the last Period 1 visit or the date of discontinuation if the subject discontinues during Period 1.

Period 2 start date will be the date/time of first administration of open-label study medication. Period 2 end date will be equal to the date of the last Period 2 visit or the date of discontinuation if the subject discontinues during Period 2.

2.2. Treatment Groups

Tables for double-blind Period 1 summarizing data by the treatment group will have columns for 'Placebo', 'Ata 10mg' and 'Ata 25mg' and a 'Total' column. The Total includes all 3 groups. Summaries will be by planned treatment. For tables summarizing data by treatment group and baseline CDR status ('Prodromal' or 'Asymptomatic at Risk') within treatment group, the baseline CDR status is the pre-dose baseline from the parent study (ALZ2002).

Tables for open-label Period 2 will have columns indicating the double-blind to open-label treatment sequence as follows: 'Placebo / Ata 5mg', 'Placebo / Ata25 mg', 'Ata 10mg / Ata 5mg', 'Ata 25mg/ Ata 25mg', and 'Total', where Total includes all 4 groups. The double-blind part of the treatment sequence is the planned treatment from double-blind Period 1. For subjects who were on placebo in Period 1, the open-label treatment is determined from ZR.ZRORRES where ZRTESTCD= "TXP". For subjects in Ata 10mg in Period 1, the open-label treatment is 'Ata 5mg', and for subjects in Ata 25mg in Period 1, the open-label is Ata 25mg.

2.3. Analysis Sets

The DB Safety Analysis Set is defined as all subjects who receive study treatment during Period 1.

The OL Safety Analysis Set is defined as all subjects who received study treatment during Period 2.

2.4. Study Days

Study day will be calculated relative to each subject's first dose in Period 1 in this study.

If the measurement date is *on or later* than the first dose date then:

study day = measurement date – first dose date + 1

If the measurement date is *earlier* than the first dose date:

study day = measurement date – first dose date.

Where applicable, study day will also be calculated relative to the first dose in the parent study ALZ2002.

For subjects in the OL Safety Analysis Set, an OL study day will be calculated relative to the first dose in Period 2.

2.5. Visit Windows

All "by-visit" analyses will be presented by scheduled study visit as recorded on the eCRF; no visit windows will be used. Unscheduled assessments will be presented in by-subject data listings. All visit names will include identifiers for the study (e.g. Day 1 ALZ2002, Week 52 ALZ2004).

2.6. Pooling Algorithm for Analysis Centers

Data from all investigative sites (centers) will be combined for analysis irrespective of the site in which the subject undergoes evaluations.

3. SUBJECT INFORMATION

3.1. Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized using descriptive statistics by treatment group: age (continuous as well as by age group [<65, 65-75, >75 years]), sex, race, ethnicity, early AD spectrum status (asymptomatic at risk or prodromal) based on CDR at baseline in ALZ2002, baseline height (HT, cm), baseline weight (WT, kg); baseline BMI calculated as WT / $(HT/100)^2$.

The number of subjects enrolled will be tabulated by country and site for the DB Safety analysis set and for the OL Safety analysis set, separately.

3.2. Disposition Information

Completion on the eCRF is not documented separately for Periods 1 and 2. The disposition for subjects in the DB Safety analysis set will be summarized for Period 1 according to the Period 1 analysis start/end dates. Subjects who did not discontinue during Period 1 and are part of the OL Safety analysis set will be considered to have completed the Period 1. Disposition for subjects in the OL Safety analysis set will be summarized separately.

3.3. Prior and Concomitant Medications

Medications received from the signing of the ICF prior to this study start and concomitantly during this study Period 1 will be tabulated for the DB Safety Analysis Set. The number and

percentage of subjects receiving each concomitant medication will be tabulated by ATC class and generic term and treatment group, where concomitant for Period 1 is defined as medications taken during Period 1 this study (excludes medications that were stopped prior to first dose of study drug in ALZ2004 or those which were started on or after the first dose of Period 2). Similar tabulations will be prepared for subjects in the OL Safety Analysis Set, where concomitant for Period 2 is defined as medications taken during Period 2 of the study (excludes medications that were stopped prior to the first dose of study drug in Period 2). Study days of the start of the concomitant medication relative to the first dose of study drug in Period 1 (for all subjects) and relative to the first dose in Period 2 (for subjects in the OL Safety analysis set) will be included in the listings.

3.4. Extent of Exposure

The total number of subjects who received study drug in Period 1 in this study will be presented by treatment group. Duration of exposure to study drug in Period 1 of this study will be summarized by treatment group. Duration of exposure will be defined as the study day (relative to start of ALZ2004) of the last Period 1 record in the exposure dataset. Tables for Period 1 exposure will be summarized by treatment group for the DB Safety Analysis Set. Similar tables will be summarized for Period 2 for the OL Safety analysis set, where duration of exposure will be defined as the date of last dose in OL Period 2 – date of first dose in OL Period 2 + 1.

3.5. Protocol Deviations

Major protocol deviations during the screening and blinded treatment periods of the study will be tabulated for the DB Safety analysis set. Major protocol deviations for the open-label period will be tabulated for the OL Safety analysis set.

4. SAFETY

The safety data will be summarized using descriptive statistics unless otherwise specified.

4.1. Adverse Events

The verbatim terms used in the CRFs by investigators to identify adverse events will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA Version 19.1 or later version) maintained by the sponsor. All reported adverse events with onset on or after the start of study treatment in Period 1 and before the start of Period 2 will be will be included in the summary tables for DB Period 1 for the DB Safety analysis set (this will also include adverse events that have worsened since baseline). For a subject who withdrew before completion of treatment Period 1, adverse events through the day of last dose of study drug plus 7 days are included as treatment-emergent for Period 1. All reported adverse events with onset on or after the start of study treatment in Period 2 through the day of last dose in Period 2 plus 7 days will be will be included as treatment-emergent in the summary tables for OL Period 2 for the OL Safety analysis set.

The number and percentage of subjects who have experienced at least 1 occurrence of the given adverse event will be summarized by system organ class, preferred term and treatment group. In addition, serious adverse events (SAEs), AEs that result in death, and AEs that lead to study

discontinuation will be summarized by system organ class, preferred term and treatment group. The summaries will be presented for the DB Safety analysis set and separately for the OL Safety analysis set.

Incidence of other treatment-emergent adverse events of special interest defined below will be summarized for the DB Safety analysis set and separately for the OL Safety analysis set.

Treatment-emergent adverse events related to abnormal liver function tests (LFTs) will be summarized. Adverse events related to abnormal LFTs are defined as follows:

- Events belonging to the MedDRA Sub_SMQ1= "Drug related hepatic disorders - comprehensive search (SMQ)".

Dermatological and ophthalmological events are identified by the investigator on the AE eCRF page and include:

- Dermatological Events
  - Lightening of hair
  - Skin coloration (hypopigmentation)

- Ophthalmological Events
  - Iris coloration (hypopigmentation)
  - Retinal changes
  - Other

The following subject data listings will be prepared. All AEs during this study, before first dose, during Period 1, during Period 2, or after last dose, (regardless of whether considered treatment-emergent), will be included in the listings. Study days relative to the first dose in Period 1 (for all subjects) and study days relative to the first dose in Period 2 (for subjects in the OL Safety analysis set) will be included in the listings.

- subjects with any AEs
- subjects with serious adverse events (SAEs)
- subjects who die
- subjects with AEs resulting in study discontinuation
- subjects with hepatic AEs
- subjects with dermatological or ophthalmological AEs.

4.2. Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test by treatment group for the DB Safety Analysis Set and the OL Safety analysis set.

Baseline for the DB Safety analysis set will be defined as the most recent (last) value taken on or prior to the day of first dose of study drug in parent study ALZ2002. Baseline for the OL Safety analysis set will be defined as the most recent (last) value taken on or before the day of first dose of study drug in OL Period 2.

Descriptive statistics will be summarized for each laboratory test at baseline and at each Period 1 post-baseline scheduled time point, and for the change from baseline, by treatment group, for the DB Safety Analysis Set. A similar summary will be presented for baseline and each Period 2 scheduled time point for the OL Safety Analysis Set.

Shifts in laboratory test values from baseline to each post-baseline scheduled time point in Period 1 will be cross-tabulated using the laboratory normal range categories (L, N, H; for below, within, and above normal ranges, respectively) for each treatment group for the DB Safety analysis set. Similar tabulations will be presented for Period 2 for the OL Safety analysis set. A listing of subjects with any laboratory results outside the normal ranges will be provided.

Potentially clinically important (PCI) hematology, chemistry, and urinalysis laboratory values will be flagged using the criteria in Attachment 1 below. A treatment-emergent (TE) PCI value for Period 1 or Period 2 is defined as a post-baseline value during Period 1 or Period 2, respectively, that meets the criteria, but the baseline value did not meet the criteria. The number and percentage of subjects with TE PCI values will be summarized separately for Period 1 and Period 2 by treatment group. A listing of subjects with any TE PCI values will be provided.

The number of subjects with at least 1 abnormal (>1xULN) postbaseline ALT or AST value in Period 1 will be summarized by treatment group for the DB Safety analysis set. The categories are shown below. A similar summary for Period 2 will be presented for the OL Safety analysis set.

AST or ALT
- <=ULN
- >ULN-<=2*ULN
- >2*ULN-<=3*ULN
- >3*ULN

Kaplan-Meier estimates of time to first occurrence of ALT elevation (>1xULN and >3xULN) in Period 1 will be presented graphically by treatment group for the DB Safety analysis set. Subjects who have an ALT elevation will be considered an “event” and the time will be the study day of the first ALT elevation in Period 1. Subjects who do not have an ALT elevation in Period 1 will be censored at the day of the last ALT measurement in Period 1. 95% confidence intervals for the quartiles of the time to event will be estimated for each treatment group using the Kaplan-Meier method. Similar analyses will be presented for Period 2 only for the “Placebo / Ata 5mg” and “Placebo / Ata 25mg” groups of the OL Safety analysis set.

The peak Period 1 TB (total bilirubin) times the upper limit of the reference range (ULRR) will be plotted against the peak Period 1 ALT times the ULRR, on a log10 scale (eDISH plot). A similar plot will be presented for Period 2.

4.3. Electrocardiogram (ECG)

The ECG parameters that will be analyzed are RR interval, PR interval, QRS interval, QT interval and corrected QT (QTc). If there is more than one value at the same time point on the same visit day for a subject, the average of these will be used for the analysis value. ECG parameters will be summarized by treatment group for the DB Safety Analysis Set and the OL Safety analysis set.

If not provided in SDTM data, QTcB and QTcF will be calculated using QT and RR interval from each time point as below, where the QT interval is measured in msec and the RR interval is measured in seconds. QTcF is the primary correction of QT interval for the heart rate.

Bazett's correction (QTcB) = $QT/RR^{1/2}$ (FDA Guidance E14 2005)

Fridericia's correction (QTcF) = $QT/RR^{1/3}$ (FDA Guidance E14 2005)

Baseline for the DB Safety analysis set will be defined as the most recent (last) measurement on or prior to the day of first dose of study drug in the parent study ALZ2002. Baseline for the OL Safety analysis set will be defined as the most recent (last) measurement on or before the day of first dose of study drug in OL Period 2.

Descriptive statistics will be summarized for each ECG parameter at baseline and at each Period 1 post-baseline scheduled time point, and for the change from baseline, by treatment group, for the DB Safety Analysis Set. A similar summary will be presented for baseline and each Period 2 scheduled time point for the OL Safety Analysis Set.

The number and percentage of subjects who are flagged with abnormal values in Period 1 will be summarized by treatment group for the DB Safety analysis set. A similar summary for Period 2 will be presented for the OL Safety analysis set. Subjects with abnormal ECG values will be presented in a data listing. The following abnormality limits will be used for observed ECG parameters.

- Heart rate: L < 50 bpm; H > 100 bpm
- PR interval: L < 120 msec; H > 200 msec
- QRS interval: L < 70 msec; H > 120 msec
- QT interval: H > 500 msec
- QTc interval: H > 450 msec
- QTc interval: L <330 msec

In addition, potentially clinically important (PCI) QTc values and changes from baseline during Period 1 for the DB Safety Analysis Set will be flagged using the criteria below. The number and percentage of subjects with PCI QTc values and changes from baseline will be summarized by treatment group. A similar summary for Period 2 will be presented for the OL Safety analysis set. A listing of subjects with any PCI QTc values and changes from baseline will be provided.

Criteria for Potentially Clinically Important QTc Values and Changes From Baseline

	Classification	
QTc change from baseline	No concern	≤30
	Concern	>30 – ≤60
	Clear concern	> 60
QTc value (Males)	Normal	≤450
	>450-480	>450 – 480
	>480-500	>480 – 500
	>500	>500
QTc value (Females)	Normal	≤470
	>470-500	>470 – 500
	>500	>500
These criteria are based on the ICH E14 Guideline		

4.4. Vital Signs

Supine and standing vital signs (systolic and diastolic blood pressure and pulse), body temperature and body weight will be summarized at each scheduled time point.

Baseline for the DB Safety analysis set will be defined as the most recent (last) measurement on or prior to the day of first dose of study drug in the parent study ALZ2002. Baseline for the OL Safety analysis set will be defined as the most recent (last) measurement on or before the day of first dose of study drug in OL Period 2.

Descriptive statistics will be summarized for each vital sign measurement at baseline and at each Period 1 post-baseline scheduled time point, and for the change from baseline, by treatment group, for the DB Safety Analysis Set. A similar summary will be presented for baseline and each Period 2 scheduled time point for the OL Safety Analysis Set.

Potentially clinically important (PCI) values and changes from baseline and incidence of orthostatic hypotension during Period 1 for the DB Safety Analysis Set will be flagged using the criteria in Attachment 1 below. The number and percentage of subjects with PCI values and changes from baseline will be summarized by treatment group. A similar summary for Period 2 will be presented for the OL Safety analysis set. A listing of subjects with any PCI values and changes from baseline will be provided.

5. PHARMACOKINETIC AND PK/PHARMACODYNAMIC RELATIONSHIP ANALYSES

None planned.

6. PHARMACODYNAMIC/BIOMARKER ANALYSES

All summaries of biomarker data will include subjects in the DB Safety Analysis Set, by treatment group and baseline CDR status. The biomarker data will be summarized using descriptive statistics unless otherwise specified. If any biomarker values are reported as being

below the LLoQ then the respective LLoQ value will be used to calculate percent baseline reduction in order to be conservative. No biomarker summaries are planned for Period 2 for the OL Safety Analysis set.

6.1. CSF

CSF samples will be obtained for measuring Aβ fragments, as well as exploratory markers, such as but not limited to BACE, sAPP fragments, t-tau/p-tau, and other biomarkers that may be down stream of amyloid. While different Aβ fragments ($A\beta_{1-37}$, $A\beta_{1-38}$, $A\beta_{1-40}$ and $A\beta_{1-42}$) will be measured, $A\beta_{1-40}$ is the most prevalent and will be the primary measure for determining the activity of JNJ-54861911.

CSF samples will be collected in ALZ2004 Period 1 at the following time points: Day 1 Predose (only if no on-treatment CSF sample was collected under the parent protocol) and Week 52.

Re-assay samples of studies ALZ1005 and ALZ2002 will be available at the following time points: ALZ1005 Baseline, ALZ1005 Day 28, ALZ2002 Baseline and ALZ2002 Day 168.

Re-assay baseline samples of ALZ1005 or ALZ2002 will be used when assessing changes from baseline. For subjects who previously participated in the ALZ1005 study, the ALZ1005 baseline will be used. For subjects who did not participate in ALZ1005, ALZ2002 baseline will be used

Descriptive statistics will be summarized for each test at Baseline, at ALZ1005 Day 28, at ALZ2002 Day 168 and at ALZ2004 Week 52, and for the percent change from baseline, by treatment group. Corresponding time profile plots (mean and individual) for the percent change from baseline will be provided.

In addition, box-whisker plots for the mean percentage change from baseline to ALZ2004 Week 52 for each CSF biomarker will be provided by treatment group and baseline CDR status.

7. CLINICAL SCALES AND FUNCTIONAL ASSESSMENT ANALYSES

7.1. Clinical Dementia Rating Scale (CDR)

The CDR assesses three domains of cognition

- Memory,
- Orientation,
- Judgment/problem solving.

and three Domains of Function:

- Community affairs,
- Home/hobbies,

- Personal care.

using structured interviews of both the study subject and a companion/informant. It is carried out by a trained rater and scored using a standard methodology. Each domain is rated on a 5-point scale of functioning as follows: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment (Personal care is scored on a 4-point scale without a 0.5 rating available).

The CDR Sum of Boxes (CDR-SB) total score is calculated at the site as the sum of the ratings from the 6 domains. A global CDR is also calculated from the ratings of the 6 domains. The CDR global score is derived from the CDR domain ratings at the site using scoring rules per *Morris, J.C. (1993)*[2].

For all CDR domain ratings, CDR-SB total score and CDR global score, a higher score indicates greater impairment.

The primary outcome of interest is the CDR-SB total score. Other outcomes of interest are the CDR domain ratings and CDR global score. These scores during Period 1 will be summarized using descriptive statistics for the DB Safety analysis set, and scores during Period 2 will be summarized for the OL Safety analysis set. Baseline for both Period 1 and Period 2 here is defined as the most recent (last) measurement on or prior to the day of first dose of study drug in the parent study ALZ2002.

In addition, progression of CDR global score after dosing in Period 1 of ALZ2004 will be summarized using descriptive statistics for the DB Safety analysis set. A similar summary for Period 2 will be presented for the OL Safety analysis set, using the original CDR baseline from the parent study ALZ2002 for baseline.

7.2. Cognitive Function Index (CFI)

The CFI is a modified version of the Mail-in Cognitive Function Screening Instrument[4], a subject- and study partner-reported outcome measure developed by the Alzheimer's Disease Cooperative Study (ADCS). Study subjects and their study partners independently rate the subject's abilities in this study before dosing on Day 1, at Weeks 24 and 52 of Period 1, and every 24 weeks in Period 2. CFI was not assessed in the parent study.

The questionnaire consists of 15 items, the first 14 of which assess the subject's perceived ability to perform high-level functional tasks in daily life and sense of overall cognitive functional ability and are scored as "yes," "maybe," and "no", and 1 additional question about whether the subject has seen a doctor in the last year about memory concerns. The first 14 item responses for the participant version are found in the QS dataset as QSCAT = "ADLS CFI PARTICIPANT" and QSTESTCD in (CFI0101, CFI0102, …, CFI0114), and for the study partner version as QSCAT = "ADLS CFI STUDY PARTNER" and QSTESTCD in (CFI0201, CFI0202, …, CFI0214). These 14 responses will be converted to corresponding numeric scores as follows: yes=1, maybe=0.5, and no/does not apply=0. The ADCS-CFI Total score is calculated as the sum of the 14 items, ranging from 0 to 14. Higher scores indicate greater impairment.

In the case of missing items, if there are < 5 (<30%) missing items, an imputed total score will be calculated as a prorated total based on the observed items:

$$14 * \frac{\text{Total score of nonmissing items}}{\text{Total number of nonmissing items}}$$

Imputed total scores will be rounded to 1 decimal place. If there are 5 or more missing items, the ADCS-CFI Total score will be missing.

Baseline for the DB Safety analysis set will be defined as the most recent (last) assessment on or prior to the day of first dose of study drug in Period 1 of this study (Day 1). Baseline for the OL Safety analysis set will be defined as the most recent (last) assessment on or before the day of first dose of study drug in OL Period 2 (expected to be the Week 52 value from Period 1).

Descriptive statistics for the ADCS-CFI Total scores (both the participant version and the study partner version) will be summarized at baseline and each scheduled visit in Period 1, and for the change from baseline, by treatment group and baseline CDR status for the DB Safety analysis set. A similar summary will be presented at baseline and each scheduled visit in Period 2 and for the change from baseline, by treatment group for the OL Safety analysis set.

8. COGNITIVE ASSESSMENT ANALYSES

8.1. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS was selected because it is a widely used measure to differentiate healthy normal subjects from those with early disease and AD patients, is predictive of functional status, correlates with the CDR, biomarker and cognition in this early population.

The RBANS is a battery of tests developed for cognitive assessment, detection, and characterization of dementia. The RBANS includes 12 subtests that measure 5 indices;

- Attention: Digit Span and Coding
- Delayed Memory: List Recall, List Recognition, Story Recall and Figure Recall
- Immediate Memory: List Learning and Story Memory
- Language: Picture Naming and Semantic Fluency
- Visuospatial/Construction: Figure Copy and Line Orientation

The raw scores from the subtests are scaled together using an RBANS conversion table to create index scores. Index scores are summed to form the Sum of Index scores. The Sum of Index Scores is converted to the Total Scale using the RBANS Conversion Table[3].

All RBANS outcome measurements are calculated at the site.

Baseline for the DB Safety analysis set will be defined as the most recent (last) assessment on or prior to the day of first dose of study drug in the parent study ALZ2002. Baseline for the OL

Safety analysis set will be defined as the most recent (last) assessment on or before the day of first dose of study drug in OL Period 2.

Descriptive statistics will be summarized for each score (Total Scale, Attention Index, Delayed Memory Index, Immediate Memory Index, Language Index, and Visuospatial/Constructional Index) at baseline (from ALZ2002) and at Weeks 24 and 52 in Period 1, and for the change from baseline, by treatment group and baseline CDR status for the DB Safety analysis set. A similar summary will be presented for Period 2 by treatment group for the OL Safety analysis set.

The change from baseline to Period 1 Week 52 for the RBANS Total Scale score will be analyzed with an ANCOVA model that includes treatment group, actual baseline CDR status and baseline score as a covariate for the DB Safety analysis set. The Least Squares (LS) means and treatment differences relative to placebo with the corresponding 95% confidence intervals will be provided.

The change from baseline at Period 1 Weeks 24 and 52 for the Total Scale score will be plotted across treatment groups by baseline CDR status to visually evaluate the dose response trend. A mean plot of the observations will be plotted at each dose level by Baseline CDR Status for the DB Safety analysis set.

The change from baseline at Period 1 Week 52 in the Total Scale score will be plotted against the change from baseline at Period 1 Week 52 in CSF Aβ1-40 for the DB Safety analysis set. Scatter plots of individual paired data will be produced. The points will be identified visually for each dose group by different colors.

8.2. Mini Mental State Examination (MMSE)

The Mini-Mental State Examination (MMSE) is a brief, validated 30-point questionnaire that is widely used to screen for cognitive impairment. The MMSE rates subjects on the following components:

- Orientation (to place and to time, 10 total),
- Registration (3 total),
- Attention and calculation (5 total),
- Recall (3 total), and
- Language (comprehension, drawing, naming, reading, repetition, writing, 9 total).

Each question is rated as 1 for a correct answer or 0 otherwise. The item scores in each component are summed to get the component score. If an item score is missing in a component, then that component score will be missing. An overall total score is obtained by summing all the item scores. The maximum total score is 30. The lower the score the more pronounced the impairment.

The primary MMSE Outcome of interest is Total Score.

In the case of missing item scores, if there are <10 (<30%) missing items, an imputed total score will be calculated as a prorated total based on the observed items:

$$30 * \frac{\text{Total number of correct answers}}{\text{Total number of nonmissing items}}$$

Imputed total scores will be rounded to 1 decimal place. If there are 10 or more missing items, the total score will be missing.

Baseline for the DB Safety analysis set is defined as the baseline in parent study ALZ2002. Baseline for the OL Safety analysis set will be defined as the most recent (last) assessment on or before the day of first dose of study drug in OL Period 2. The MMSE Total Score will be summarized at baseline and Period 1 Week 52, and for the change from baseline, by treatment group and baseline CDR status for the DB Safety analysis set using descriptive statistics. A similar summary will be presented for Period 2 by treatment group for the OL Safety analysis set.

The change from baseline to Period 1 Week 52 for the MMSE Total Score will be analyzed with an ANCOVA model that includes treatment group, actual baseline CDR status and baseline score as a covariate for the DB Safety analysis set. The Least Squares (LS) means and treatment differences relative to placebo with the corresponding 95% confidence intervals will be provided.

The change from baseline at Period 1 Week 52 for the MMSE Total Score will be plotted across treatment groups and baseline CDR status to visually evaluate the dose response trend. A mean plot of the observations will be plotted for each dose level by Baseline CDR Status for the DB Safety analysis set.

The change from baseline at Period 1 Week 52 in the MMSE Total Score will be plotted against the change from baseline at Period 1 Week 52 in CSF Aβ1-40 for the DB Safety analysis set. Scatter plots of individual paired data will be produced. The points will be identified visually for each dose group by different colors.

8.3. California Verbal Learning Test – Second Edition (CVLT-II)

The CVLT-II is a face-to-face comprehensive neuropsychological measure of verbal memory in individuals 16 to 89 years old, designed to quantify components of verbal learning, retention and retrieval. This test will be administered only to subjects who had completed it in the parent protocol ALZ2002. This test was performed on Day 1, prior to dosing in ALZ2002, and at Week 12 in Period 1 of this study ALZ2004 (baseline).

The following scores will be derived: Immediate recall, Short-delay recall, Long-delay recall, All recall types, and Long-delay recognition. These scores were already derived at baseline in ALZ2002 by summing the scores from the ALZ2002 tests listed in the table below. The scores for Period 1 Week 12 in ALZ2004 will be derived by summing the scores of the corresponding ALZ2004 tests listed below.

Derived Test Name	Test Name (FTTEST) in ALZ2002	Test Name (FTTEST) in ALZ2004
1. Immediate recall	CVLT01-List B Free Recall Immediate	List B Free Recall
1. Immediate recall	CVLT01-List A Free Recall Immed Total	Trial 1-5
2. Short-delay recall	CVLT01-List A Cued Recall Short Delay	Short-Delay Cued Recall
2. Short-delay recall	CVLT01-List A Free Recall Short Delay	Short-Delay Free Recall
3. Long-delay recall	CVLT01-List A Cued Recall Long Delay	Long-Delay Cued Recall
3. Long-delay recall	CVLT01-List A Free Recall Long Delay	Long-Delay Free Recall
4. All recall types	CVLT01-Cued Recall Intrusions	Cued-Recall Intrusions
4. All recall types	CVLT01-Free Recall Intrusions	Free-Recall Intrusions
4. All recall types	CVLT01-Total Intrusions	Total Intrusions
4. All recall types	CVLT01-Total Repetitions	Total Repetitions
5. Long-delay recognition	CVLT01-List A Yes/No False-Positives	Long-Delay Recognition False-Positives
5. Long-delay recognition	CVLT01-List A Yes/No Hits	Long-Delay Recognition Hits

Descriptive statistics will be summarized for each derived score at baseline and at Period 1 Week 12, and for the change from baseline, by treatment group and baseline CDR status, for the DB Safety analysis set.

9. REFERENCES

1. SAS Institute, Inc., Version 9.4, Cary, NC.
2. Morris, J.C. (1993). The clinical dementia rating (CDR): Current version and scoring rules. Neurology, 43(11), 2412-2414.
3. Randolph, Christopher. *RBANS Repeatable Battery for assessment of Neuropsychological status.*
4. Walsh SP, Raman R, Jones KB, Aisen PS; Alzheimer's Disease Cooperative Study Group. ADCS Prevention Instrument Project: the Mail-In Cognitive Function Screening Instrument (MCFSI). Alzheimer Dis Assoc Disord. 2006; 20(4 Suppl 3):S170-S178.

ATTACHMENTS

1. PCI CRITERIA FOR CLINICAL LABORATORY RESULTS AND VITAL SIGNS

Test	Criteria for Low PCI Values	Criteria for High PCI Values
Hematology		
WBC Leukocytes (x10E9/L)	<3	>16

Eosinophils (x10E9/L)	NA	> 0.6
Lymphocytes (x10E9/L)	<0.8	NA
Monocytes (x10E9/L)	NA	> 1.0
Neutrophils, Segmented (x10E9/L)	<1.5	> 8.0
Platelets (x10E9/L)	< 75	> 700
Hematocrit (fraction)	<0.3	> 0.5 females, > 0.55 males
Hemoglobin (g/L)	value <100 or change from baseline <= - 20	>165 females, >185 males
MCV (fL)	< 75	>105
Chemistry		
Serum Albumin (g/L)	< 30	NA
Alkaline Phosphatase (U/L)	NA	> 2.5 ULN
ALT (U/L)	NA	> 3 ULN
AST (U/L)	NA	> 3 ULN
Bicarbonate (mmol/L)	< 17	> 32
Direct Bilirubin (umol/L)	NA	> 1.5 ULN
Total Bilirubin (umol/L)	NA	> 1.5 ULN
BUN (mmol/L)	NA	> 1.5 ULN
Calcium (mmol/L)	< 2.0	> 2.7
Chloride (mmol/L)	< 94	> 112
Cholesterol (mmol/L)		
Creatine Kinase (U/L)	NA	> 1.5 ULN
Creatinine (umol/L)	NA	> 1.5 ULN
GGT (U/L)	NA	> 75
Glucose (mmol/L)	< 3.9	> 5.6
HDL Cholesterol (mmol/L)		
LDH (U/L)		
Phosphate (mmol/L)	< 0.7	> 1.7
Potassium (mmol/L)	< 3	> 5.5
Protein (g/L)	< 60	> 80
Sodium (mmol/L)	< 135	> 145
Triglycerides (mmol/L)		
Urate (umol/L)	< 150	> 500
Urinalysis		
pH	< 4	> 8
Specific Gravity	NA	> 1.035
Vital Signs		
Systolic BP (mmHg)	< 90	>180
Diastolic BP (mmHg)	<50	>105
Pulse (beats/min)	<50	>120
Temperature (C)	<36	>38

Weight (kg)	Decrease of 10% relative to baseline	Increase of 10% relative to baseline
Orthostatic Hypotension	Decrease in systolic (>20 mm Hg) or diastolic (>10 mm Hg) blood pressure after standing for at least 2 minutes relative to supine position with an increase in pulse rate of >15 beats per minute.	