A 12-Month, Open-Label Safety Study of Simufilam followed by a 6-Month Randomized Withdrawal and 6 Additional Months Open- Label in Mild-to-moderate Alzheimer's Disease Patients

NCT #: 04388254

v3.0 December 8, 2023

Statistical Analysis Plan for Final Analysis

PTI-125-04

Statistical Analysis Plan

for Final Analysis

PTI-125-04

v1.0 December 21, 2022
v2.0 May 26, 2023
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1 Introduction

1.1 Purpose of the Study

The purpose of this Statistical Analysis Plan (SAP) is to provide a thorough description of the statistical methods used to analyze the data and the presentation of the study results consistent with protocol PTl-125-04, Version dated June 11, 2021: "A 12-Month, Open-Label Safety Study of Simufilam followed by a 6-Month Randomized Withdrawal and 6 Additional Months Open-Label in Mild-to-moderate Alzheimer's Disease Patients." Simufilam is an investigational drug candidate under development by the protocol Sponsor, Cassava Sciences, Inc.

Results from these analyses will be included in the final clinical study report for PTI-125-04, and may also be utilized for regulatory submissions, manuscripts, or to obtain additional guidance on the design and conduct of large, on-going Phase 3 studies of simufilam in Alzheimer's disease.

Post-hoc exploratory analyses not identified in this SAP may be performed at the request of the Sponsor, should further examination of study data be required. These analyses will be clearly identified, where appropriate, in the final clinical study report.

This SAP includes details of data handling procedures and statistical methodology. The final statistical analysis will proceed in accordance with this SAP as approved by Cassava Sciences, Inc., Axiom Real-Time Metrics, and Pentara Corporation. Any material deviation from this SAP will be documented in the final Clinical Study Report (CSR). Any material deviations from methods described in the protocol are also detailed and explained in this SAP.

This version of the SAP will be finalized and approved by the Sponsor, Axiom, and Pentara prior to database lock. Statistical programming of study data will be initiated as study data accumulates to ensure analysis program are setup and readily available prior to statistical delivery.

1.2 SAP Modification

Version 1.0 and 2.0 of the SAP were used for analyses of the open-label (OL) and randomized withdrawal (RW) phases. The current version. 3.0, will be used for the analysis performed on the final data and the CSR submission.

1.3 Study Objectives

The overall study objective is to assess the long-term safety and tolerability of simufilam.

This study has separate sets of objectives for the OL and RW phases. Safety and tolerability are the primary objectives of the OL phase. The primary objective of the RW phase is to assess patient response to blinded, randomized drug withdrawal.

Because drug safety in non-responders can be a critical component of a drug's risk-reward assessment, all patients who completed the 12-month OL phase were eligible to enter the RW phase, regardless of whether they previously showed an apparent response (or not) to open-label drug treatment.

Some study objectives overlap in the OL and RW phases. Hence, objectives are summarized separately below for the OL and RW phases, and for objectives spanning multiple phases. All objectives apply to mild-to-moderate Alzheimer's Disease (AD) patients, 50-85 years of age.

Objectives for the Open-label (OL) phase

- Assess the long-term safety and tolerability of OL treatment with simufilam 100 mg b.i.d. during 12-month repeat-dose oral administration.
- Assess mean changes from baseline on MMSE and compare those changes between patients with mild vs moderate AD.

Objectives for the Randomized Withdrawal (RW) phase

- Assess the safety and tolerability of treatment with simufilam 100 mg b.i.d. versus matching placebo over the 6-months study period.
- Assess patient response to blinded, randomized drug withdrawal on ADAS-Cog11.

Objectives Spanning Overall Study

Exploratory objectives tested across multiple phases are to:

- Characterize the safety and tolerability of simufilam during and up to 24 months of treatment.
- Assess mean changes from baseline on biomarkers and compare those changes between patients with mild vs moderate. For CSF biomarkers, change from baseline to M6 or M12 will be calculated. Plasma biomarkers will be analyzed for change from baseline to M6 and M12 for the OL phase and from M12 to M18 for the RW phase.

Note: All biomarker assessments in this study are exploratory endpoints that are not patient safety related, are 'Research Use Only' products, and, hence, are not intended to be compliant with FDA's Quality System Regulation (QSR) or ISO equivalent.

- Compare mean changes from baseline on MMSE and ADAS-Cog11 during 24 months of treatment between patients who took simufilam continuously vs those who had interrupted dosing (placebo in the RW phase) (combines data from OL, RW and follow-up phases).

1.4 List of abbreviations

AD	Alzheimer's Disease
ADaM	Analysis Data Model
ADAS-Cog	Alzheimer's Disease Assessment Scale
AE	Adverse Event
ANCOVA	Analysis of Covariance
BMI	Body mass index
CSF	Cerebrospinal Fluid
CSI	Cassava Sciences, Inc.
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
ET	Early Termination
FAS	Full Analysis Set
FDA	Federal Drug Association
IE	Inclusion/Exclusion Criteria
Kg	Kilogram(s)
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram(s)
MMSE	Mini-Mental State Examination
MMRM	Mixed model repeated measures
RTF	Rich Text Format
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SI	International System of Units
SOC	System and Organ Class
SP	Safety Population
TEAE	Treatment-emergent AE
TLF	Tables, Listings, and Figures
VS	Vital Signs
WHO-DD	World Health Organization Drug Dictionary

2 Background and Design

2.1 Background

This study is for patients who 1) completed PTI-125-02, a multi-center, randomized, double-blind, placebo-controlled, study of simufilam in mild-to-moderate AD patients, 50-85 years of age; 2) completed PTI-125-03, a 1-month open-label PK and biomarker study of simufilam at 100 mg b.i.d.; and, 3) are newly enrolled.

2.2 Study Design

All patients received simufilam 100 mg b.i.d. as coated oral tablets.

The first 12 months is an open-label treatment of simufilam 100 mg b.i.d. Month 12 to Month 18 is a RW phase in which patients who completed OL treatment are randomized (1:1) to simufilam 100 mg b.i.d. or matching placebo. Month 18 to Month 24 will be an additional 6 months of open-label simufilam 100 mg b.i.d.

Simufilam and placebo will be administered as coated oral tablets. Patients who were enrolled prior to the protocol amendment could continue upon reconsenting to the RW and final 6-month open-label portion.

All patients provided consent to enroll into this study. Patients reported to the clinic in the morning of Day 1. Prior to dosing, patients completed the following baseline measures: ADAS-Cog11, C-SSRS, ECG, vital signs, clinical labs, urinalysis, listen to heart and lungs, and MMSE. A blood sample was collected for plasma-based biomarkers.

Patients returned to the clinic every month through Month 3 and every 1.5 months through Month 12. Visits on Months 4.5, 7.5 and 10.5 included vital signs, listening to heart and lungs, AE monitoring, C-SSRS and drug dispensation and accountability only. Visits at Months 4.5, 7.5 and 10.5 could be performed by telemedicine, based on the judgement of the Investigator. Only AE-monitoring and C-SSRS assessment could be performed remotely. After Month 12, visits occurred on Months 13, 15, 18, 21 and 24. Patients completing Month 12, and who chose to continue into the RW phase of the study, prior to availability of drug supply for the RW phase continued with active treatment until drug supply was ready and therefore had an additional "Withdrawal Day 1" visit before resuming with the Month 13 visit one month later. Collection of saliva for genetic testing occurred at Month 15.

Blood draws for clinical laboratory testing and urine collection for urinalysis were performed at Day 1 and Months 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24. Safety assessments of vital signs and listening to heart and lungs were conducted at Months 2, 4.5, 7.5 and 10.5 visits.

ECGs were conducted on Day 1 and Months 1, 6, 12, 18 and 24. For plasma biomarkers (NFL and GFAP), plasma samples will be analyzed for Day 1, collected prior to dosing, and at Months 6, 12, and 18. CSF biomarkers (NfL, neurogranin, tau, p-tau181, TREM2, Aβ42, HMGB1 and YKL40) may be collected at screening. For the first 50 patients who provided a screening CSF sample, an additional CSF sample was to be collected at Month 6 or Month 12 (25 patients each Month 6 and Month 12). A Month 18 CSF sample was optional for patients who provided a Month 6 or Month

12 CSF sample. These samples will be used to assess CSF biomarker changes.

2.3 Inclusion / Exclusion Criteria

The inclusion and exclusion criteria are defined in the final protocol (Section 5.2 and 5.3) and apply to all patients who consent to the study. Key features of the study population included that patients were Ages ≥ 50 and ≤ 85 years, with a clinical diagnosis of dementia due to possible or probable AD, MMSE-2 score ≥ 16 and ≤ 26 at screening, OR if > 26, must have evidence of AD pathology such as a prior CSF total tau/Aβ42 ratio ≥ 0.28, an amyloid positive PET scan or hippocampal volume loss consistent with AD.

2.4 Study Drug Dosing

Investigational simufilam was supplied by Cassava Sciences as coated tablets in 70-, 188-, or 200-count bottles. Several days of extra tablets were included in each bottle to allow flexibility of scheduling visits. Simufilam tablets were to be taken twice daily, with or without food.

2.5 Sample Size

220 patients were enrolled in this study. Of those patients, 43 dropped out during the OL phase, and 21 patients who had consented only to the OL (20 prior to the protocol amendment and 1 patient who refused to complete the scales) did not reconsent to continue.

2.6 Schedule of Events

The schedule of assessments is presented in Table 1.

Table 1. Schedule of Events for final analysis

PROCEDURE	Screen Visit 1	Screen Visit 2	DAY 1	Month 1	Months 2, 4.5, 7.5 & 10.5	Months 3, 9, 15 & 21	Month 13	Months 6 & 18	Month 12 & 24	(With-drawal Day 1)
Informed Consent	X								(X) [a]	
Medical histories	X									
ECG	X		X	X		X		X	X	
CT scan	(X)									
Vital signs	X		X	X	(X)	X	X	X	X	
Physical examination	X		*	*	(*)	*	*	*	X	
Biochemistry, hematology, urinalysis	X		X	X	Month 2 only	X		X	X	
MMSE-2	X								X	
Cheek saliva swab for genetic testing						Month 15 only				
HCV, HBsAg & HIV screen	X									
Urine drug screen	X									
Drug dispensation			X	X	X	X		X	X	X
Adverse events			X	X	X	X	X	X	X	
Blood draw for biomarkers			X			X		X	X	
CSF draw		(X) [b]						(X) [c]	(X) [c]	
ADAS-Cog			X	X		X	X	X	X	X
C-SSRS	X		X	X	X	X	X	X	X	X

( ) indicates performed per investigator judgement or not for all patients
* Listen to heart and lungs
a Reconsenting at Month 12 only for patients who did not initially consent for a 2-year study.
b Patients who have a prior amyloid PET or other confirmation of AD can bypass this baseline CSF draw
c Only for patients with a baseline CSF. Patients with a baseline CSF have the option to do a Month 6 or 12 CSF draw. Month 18 CSF draw is an option only for patients who provided Month 6 or 12 CSF.
NB: Withdrawal Day 1 is only for patients who complete Month 12 prior to drug supply availability for the RW.

3 Considerations for Data Analysis

3.1 Overview

Analyses are specified in sections 4 for overall population, 5 for Open-label (OL) phase, 6 for RW phase, and section 7 describes analyses that span the OL follow-up to RW phase. Nevertheless, some considerations apply to all phases, and these general considerations are specified in the next subsection.

3.2 General Considerations that Apply to All Phases

Analysis Populations

Three analysis sets are defined for each phase of the study.

- The Full Analysis Set (FAS) includes all patients who receive at least one dose of study treatment and have evaluable efficacy records at baseline and post-baseline visits.

- The Per Protocol Analysis Set (PP) is the same as the FAS minus patients with major violations of protocol inclusion or exclusion criteria, e.g., other or interfering neurologic disorders such as posterior cortical atrophy, frontotemporal dementia, multiple psychiatric diagnoses, taking anxiolytics, or significant history of cardiovascular disease. PP also excludes patients who refused assessments for one or more visits and patients who were < 65% compliant by pill counts.

- The Safety analysis set will include all patients who receive at least one dose of the study treatment. All safety analyses will be based on the Safety population. Patients will be analyzed as treated.

Defining Mild vs Moderate Baseline Severity

For the purposes of analyses in all phases of the study, mild AD is defined as baseline MMSE ≥ 21, and moderate AD as baseline MMSE ≤ 20.

Management of Analysis Data

All tables, listings and figures will be presented in landscape format. All outputs will be sent to CSI as electronic files in Rich Text Format (RTF) format documents.

Definition of Analysis Timepoints

Scheduled analysis visits are visits upon scheduled time points as specified in Table 1 Schedule of Time and Events.

Scheduled analysis visits during the study period will be windowed to the nearest scheduled visit within the same phase.

Unscheduled visits are visits with data not collected at scheduled time points. Unscheduled visits will be windowed to the nearest scheduled visit as described above.

For the purposes of calculating change from baseline in the tables, if there is an unscheduled visit with a value and the visit BEFORE the unscheduled visit (i.e., scheduled visit) does not have a value for that assessment, the value associated with unscheduled visit can be used. Else, disregard the unscheduled visit, if scheduled visit is available and has a value.

There will be one valid value of assessment kept for each scheduled analysis visit in summary / analysis statistics. All unscheduled visits will be included as collected in eCRF in listings.

Handling of Missing Data and Partial Dates

Missing data will not be imputed for the purpose of primary inference. Imputation of missing data may be used as a sensitivity analysis. All data recorded on the electronic case report form (eCRF) will be included in data listings that will accompany the clinical study report, as applicable.

For qualitative parameters, a category with the number of patients with missing values will be presented where applicable.

If complete Adverse Event (AE) start date is missing and AE end date is on or after the date of first dose, then the AE will be counted as a treatment emergent AE (TEAE) for the study.

If an AE has a partial missing start or stop date, the following rules will be used for imputation:

- If year is present but month and day are missing, impute start date as first dose date if the year is the same as the year of first dose date, otherwise January 1 of that year and impute stop date as last dose date if the year is the same, otherwise December 31 of that year.

- If year and day are present but month is missing, impute start month as first dose date month if AE start day greater than or equal to first dose day and if the year is the same, otherwise January and impute stop month as last dose date month if AE end day less than or equal to last dose day and if the year is the same, otherwise December of that year.

- If year and month are present but day is missing, impute start date as first dose day if the year and month are the same as the year and month of first dose date, otherwise first day of that month and impute stop date as last dose day if year and month are the same, otherwise last day of that month.

Coding Conventions for Events, Medical History, and Medications

All adverse events and medical history indication will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) (version 24.0)

All Concomitant medications will be coded using World Health Organization (WHO) Drug Global C3 (version Mar 1, 2021 C3 format).

Analysis Software

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS 9.4 for Windows. If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes.

Study Data

Study data identified in the schedule of events are collected, and source verified, on the electronic data capture tool: Axiom Fusion eClinical Suite (Axiom, Toronto, ON, Canada).

All study data will be formulated into regulatory compliant data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Observed study data will be mapped to the CDISC Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture. All planned analyses will be performed using the ADaM data sets developed for this study.
The following Implementation Guides will be referenced for the configuration of SDTM and ADaM datasets:

- SDTM Model 1.7 and SDTM Implementation Guide (SDTM IG) version 3.3 will be used.
- ADaM Model 2.1 and ADaM Implementation Guide (ADaM IG) version 1.3 will be used.

Statistical Summaries

All statistical tests in all phases of the study will be two-sided and p-values of less than or equal to 0.05 will be considered statistically significant.

All p-values will be rounded and displayed in 3 decimal places. If a p-value less than 0.001 occurs, it will be shown in tables as <0.001.

Descriptive summaries of variables will be provided where appropriate. For continuous variables, the number of non-missing values (n) and the median, mean, standard deviation, minimum, and maximum will be tabulated by treatment. For categorical variables, the counts and proportions of each value will be tabulated by treatment.

Data will be presented as listings where applicable. Data not patient to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings.

4 Analyses Spanning Overall Study

For the below analyses, it will be summarized by overall.

4.1 Patient disposition

Patient disposition will be summarized by overall and will include:

- The number of patients screened
- Number of subjects screen failed
- Number of subjects enrolled
- Number of subjects in the Safety analysis set
- Number of subjects enrolled - Period 1
- Number of subjects completed - Period 1
- Number of subjects enrolled - Period 2
- Number of subjects completed - Period 2
- Number of subjects enrolled - Period 3
- Number of subjects completed - Period 3
- Total number of subjects having early termination – all periods
- Reason Subject early termination (as per the CRF)

A patient level data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

4.2 Protocol Deviations

All protocol violations will be captured directly in Fusion and will be presented in a data listing.

4.3 Demographics and Baseline Characteristics

The demographics consist of age (year), sex, race, and ethnicity. The baseline characteristics consist of baseline height (cm), baseline weight (kg), and baseline body mass index (BMI) (kg/m^2). Body mass index is calculated as (body weight in kilograms) / (height in meters)^2.

Patient demographic data and baseline characteristics will be summarized descriptively overall. The demographic data and baseline characteristics will be summarized based on the safety population.

4.4 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

Patient medical history data including specific details will be presented in a listing.

4.5 Concomitant Medications

All medication data will be presented in listings. The number (%) of patients taking AD symptomatic medication at baseline (day 1) and throughout the study will be summarized.

4.6 Treatment Compliance and Extent of Exposure

Study medication compliance will be calculated based on the numbers of tablets dispensed minus the number of tablets returned divided by the expected number of tablets based on the duration of the patient's participation in the study and will be summarized as continuous and categorical variables. Compliance will be summarized as a continuous outcome using mean, SD, median, min, and max. For the categorical analysis, a patient will be considered compliant if the amount of medication taken is within the range of 75% - 125% of the amount of medication planned to be taken.

Total number of days the patient is on study drug will be summarized as a continuous variable. The Days a patient is on study drug will be calculated as the number of days from date of first dose to date of last dose plus 1.

Treatment compliance will be summarized overall.

4.7 Safety Analysis

Adverse Events

Treatment emergent AEs (TEAEs), defined as AEs that first occurred or worsened after first dose, will be summarized overall. Summary of TEAEs occuring in the Open-label phase (D1-M12 and M18-M24) will be summarized in one group . TEAEs occurring in Double-blind (RW) phase (M12-M18) will be summarized in other group. All the listings mentioned below to be provided for both the groups. The incidence of TEAEs will be reported as the number (percent) of patients with TEAEs within System Organ Class (SOC) and Preferred Term (PT). Patients will be counted only once within a SOC and PT, even if the patient experienced more than one TEAE within a specific SOC and PT. The number (percent) of patients with TEAEs will also be summarized by maximum severity and relationship. The denominators for calculating the percentages for summaries will be based on the number of patients in the analysis population enrolled to each group.

The following types of summary will be provided for Incidence of TEAEs:

- Treatment Emergent Adverse Events by System Organ Class and Preferred Term;
- Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity;
- Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relationship to Study Drug;

The annualized incidence rate of AEs per person-years at risk, calculated as (365.25*number of AE occurrences)/(total treatment period with patients at risk of AE), will also be reported by most prevalent PT in the SOC.

The total period at risk for each patient will be defined as the period from first dose of study treatment to the date of the End of Treatment (EOT) (Month 12) or Early Termination (ET) visit for prematurely treatment discontinued patients. Annualized incidence rates will be expressed in terms of events per 100 patient years exposure.

Vital Signs

For Months 6, 12, 18, and 24, summary statistics will be provided (study population size, mean, SD, minimum, median, and maximum) for each vital sign parameter, by treatment group and overall. Summary statistics for change from baseline values will also be presented. Numbers and percentages of patients with abnormal values will be included.

ECG

The 12-lead ECG tests will be summarized by treatment group and overall using qualitative statistics per each scheduled visit. The summary will include the number and percentage of patients with test values classified as normal, abnormal (clinically significant), abnormal (not clinically significant) and unevaluable.

Laboratory Data

For months 6. 12, 18, and 24, summary statistics will be provided (study population size, mean, SD, minimum, median, and maximum) for each laboratory test and their change from baseline by treatment group and overall, along with their change from baseline screening values will be presented overall, for each scheduled visit. Numbers and percentages of patients with abnormal values will be included.

Physical Examination

Full physical examination data will be listed overall, by enrollment group and patient only.

5 Analysis of Open-Label Phase

The following efficacy analyses will be applied to data from the OL phase (D1-M12).

5.1 Efficacy Analysis

General Considerations

Efficacy and biomarker analyses will be based on the FAS analysis set. No adjustments for multiple comparisons will be made. Baseline values for each endpoint are defined as the last non-missing value taken on or prior to Day 1.

Unless otherwise specified, for continuous endpoints that are scheduled to be assessed at only 1 post-baseline visit (MMSE-2), mean changes from baseline will be analyzed using ANCOVA. The analysis will include the categorical, fixed effect of enrollment group (mild vs. moderate AD) along with the continuous, fixed covariate of baseline value of the endpoint being analyzed (baseline). Significance tests comparing endpoint LSMEANS by enrollment group (mild vs moderate) will be based on least-squares means. Significance of within-group mean changes from baseline will also be reported.

Biomarker exploratory endpoints

Biomarker endpoints to be analyzed may include: 1) CSF Aβ42, 2) CSF tau 3) CSF p- tau181, 4)

CSF neurofilament light chain, 5) CSF neurogranin, 6) CSF sTREM2, 7) CSF YKL40 8) CSF HMGB1 9) plasma neurofilament light chain, 10) plasma GFAP, or other non-safety related exploratory biomarkers of disease.

Plasma biomarker data may be analyzed with the MMRM model described above. CSF biomarker data may be analyzed by descriptive statistics.

Note: All biomarker assessments in this study are exploratory endpoints that are not patient safety related; are 'Research Use Only' products; and, hence, are not intended to be compliant with FDA's Quality System Regulation (QSR) or ISO equivalent.

Clinical endpoints

The ADAS-Cog11 will be analyzed using the MMRM model described above. MMSE will be analyzed by ANCOVA.

6 Analysis of Randomized Withdrawal Phase

The following efficacy analyses will be applied to data from the RW phase, which begins after the month 12 assessment and continues through month 18.

These analyses are similar to the analyses from the Open-Label phase except:

1) treatment group replaces enrollment group in the analysis models
2) baseline value is defined as the last non-missing value at or prior to month 12; or, for patients who were maintained on open-label treatment beyond month 12, baseline is defined as the last non-missing value at or prior to the withdrawal day 1 assessment.

6.1 Efficacy Analysis

General Considerations

The FAS will be the primary data for efficacy analyses.

The primary efficacy estimand for the RW phase is

- Treatment regimen of interest:
  simufilam treatment for 6 months after OL treatment with simufilam for 12 months vs placebo treatment for 6 months after OL treatment with simufilam for 12 months

- Population:
  As defined by inclusion / exclusion criteria

- Variable/Endpoint
  ADAS-Cog11

- Summary Measure

  Difference between treatments in mean change from baseline (month 12) to endpoint (month 18, i.e. month 6 of RW Phase)

- Intercurrent events (ICE) strategy

  The primary ICE of interest is early discontinuation of study drug, particularly for lack of efficacy. Given the RW phase is preceded by 12 months of OL treatment with simufilam, most patients entering the RW phase will have already demonstrated tolerability to simufilam; hence, discontinuations due adverse events are expected to be minimal. Discontinuations for lack of efficacy are likely given patients knowledge that the likelihood of being on placebo = 50%.

  Discontinuations for lack of efficacy are consistent with a missing at random (MAR) mechanism and therefore a hypothetical strategy is relevant and meaningful. Therefore, a hypothetical strategy will be used to estimate the treatment effect as if the ICE if early discontinuation had not occurred.

Unless otherwise specified, for continuous endpoints that are scheduled to be assessed at > 1 post-baseline visit, mean changes from baseline will be analyzed using a restricted maximum likelihood (REML)-based repeated measures approach (MMRM). The MMRM analysis assumes an MAR mechanism. The analysis will include the categorical, fixed effects of treatment group and Visit, along with the continuous, fixed covariate of baseline value of the endpoint being analyzed (baseline), baseline MMSE score, and the interactions of treatment group, baseline, and baseline MMSE with Visit. An unstructured (co)variance structure will be used to model the within-patient errors. If this analysis fails to converge, the following structures will be tested in this order, with the first structure yielding convergence to be used as the appropriate structure for that variable: heterogeneous Toeplitz (TOEPH), heterogeneous compound symmetric (CSH), and compound symmetric (CS). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Significance tests comparing mean changes from baseline by treatment group will be based on least-squares means. Significance of within-group mean changes from baseline will also be evaluated.

Biomarker Endpoints

Biomarker endpoints to be analyzed may include: 1) CSF Aβ42, 2) CSF tau 3) CSF p- tau181, 4) CSF neurofilament light chain, 5) CSF neurogranin, 6) CSF sTREM2, 7) CSF YKL40 8) CSF 1) plasma neurofilament light chain, 2) plasma GFAP.

Plasma biomarker data may be analyzed with the MMRM model described above.

Clinical Endpoints

The ADAS-Cog11 will be analyzed using the MMRM model described above.

7 Analysis of Follow up to Randomized Withdrawal Phase (Open-label)

The follow up phase is defined as beginning after the month 18 Visit through the month 24 assessment. The following efficacy analyses will be applied to the follow up data.

7.1 Efficacy Analysis

The efficacy analyses will be ADAS-Cog11 using the FAS. The first analysis will be change in ADAS-Cog11 from Month 12 to Month 24 by Treatment, Visit, and mild vs. moderate status. The second analysis will be change in ADAS-Cog 11 from Day 1 to Month 24 by Treatment (i.e. continuous vs. interrupted), Visit, and mild vs. moderate status (mild vs. moderate here based on OL baseline).

The primary comparison of interest from these analyses is the magnitude of the treatment effect at month 18 vs month 24. Maintenance of the treatment effect seen at the end of the RW phase (month 18) throughout the follow up phase (month 24) when all patients are on active drug would be consistent with a disease modifying effect. In contrast, appreciable diminution of the treatment effect when placebo-treated patient switch to active drug would be consistent with a symptomatic treatment effect.

8 Approvals:

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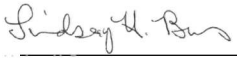

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