Study Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, 76-week Study Evaluating the Safety and Efficacy of Two Simufilam Doses in Subjects with Mild-to-Moderate Alzheimer's Disease

ClinicalTrials.gov ID: NCT05026177

Final Statistical Analysis Plan, Version 1.0, dated 28-Feb-2025

Statistical Analysis Plan

Sponsor	Cassava Sciences, Inc.
Protocol Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 76-Week, Study Evaluating the Safety and Efficacy of Two Doses of Simufilam in Subjects with Mild-to-Moderate Alzheimer's Disease.
Protocol Number:	PTI-125-06
Premier Research PCN:	CASA215435
Document Version:	Version 1.0
Document Date:	28-Feb-2025

Approvals

Role	Signatures
Premier Research	Print Name: [redacted] Senior Biostatistician
	Sign Name: 
Premier Research	Print Name: [redacted] Senior Principal Biostatistician
	Sign Name: 
Pentara Corporation	Print Name: [redacted] Distinguished Biostatistician
	Sign Name: 
Cassava Sciences, Inc.	Print Name: [redacted] Chief Medical Officer
	Sign Name: 

Document History

SAP Version	Approval Date	Change	Rationale

Table of Contents

List of Tables

List of Abbreviations

Abbreviation	Definition
AD	Alzheimer's disease
ADAS-Cog12	12-item Alzheimer's disease assessment scale – cognitive subscale
ADCS-ADL	Alzheimer's disease cooperative study – activities of daily living
AE	adverse event
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
ATC	anatomical therapeutic chemical
ASA	American Statistical Association
BID	twice daily
BMI	body mass index
CDISC	Clinical Data Interchange Standards Consortium
CDR-GS	clinical dementia rating - global score
CDR-SB	clinical dementia rating – sum of boxes
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CS	clinically significant
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
DSMB	data safety monitoring board

Abbreviation	Definition
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
ED	early discontinuation
EDC	electronic data capture
ET	early termination
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
GCP	code of good clinical practice
GDS	Geriatric Depression Scale
iADRS	integrated Alzheimer's disease rating scale
ICH	International Conference on Harmonization
ID	identification
IRT	interactive response technology
LS	least squares
MAR	missing at random
MedDRA	medical dictionary for regulatory activities
ITT	intent-to-treat
MMRM	mixed model for repeated measurements
MMSE	mini-mental state exam
MNAR	missing not at random
MRI	magnetic resonance imaging

Abbreviation	Definition
NCS	not clinically significant
NE	neurological examination
NPI or NPI-10	neuropsychiatric inventory, 10-item
PE	physical exam
PET	positron emission tomography
PK	pharmacokinetic
PT	preferred term
RSS	Royal Statistical Society
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SPA	FDA special protocol assessment
SD	standard deviation
SDV	source data verified
SE	standard error
SI	international system of units
SOC	system organ class
SOP	standard operating procedures
REML	restricted maximum likelihood
TEAE	treatment-emergent adverse event
TLF	tables, listings and figures

Abbreviation	Definition
WHO-DD	World Health Organization drug dictionary
ZBI	Zarit Burden Interview

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Cassava Sciences' protocol number PTI-125-06, A phase 3, Randomized, Double-Blind, Placebo Controlled, Parallel-Group, 76-Week Study Evaluating the Safety and Efficacy of Two Doses of Simufilam in subjects with Mild-To-Moderate Alzheimer's Disease, dated 06-FEB-2023 (version 3.0). Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials (ICH, 1998). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association (ASA, 2018) and the Royal Statistical Society (RSS, 2014), for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an a priori plan. It will be approved before any unblinded inferential or descriptive analysis of data pertaining to Cassava Science's study PTI-125-06.

This document does not include the details of the planned analyses for the external Data Safety Monitoring Board (DSMB). The schedule of planned analyses is described in the DSMB charter and separate shells for tables, listings, and figures (TLF) are prepared for the DSMB meetings.

Descriptive summary tables for efficacy endpoints will generally include: number of participants with data, mean, standard deviation, median, 25% percentile, 50% percentile, 75% percentile, minimum and maximum. Inferential efficacy summary tables will include within group mean changes from baseline along with the difference between groups in mean change and the associated standard errors and p values.

Baseline is defined as the most recent non-missing measurement collected prior to the first dose.

2. Overall Study Design and Plan

2.1. Overall Design

The original plans for the study are detailed in the following paragraphs. However, this study was stopped early. The blinding and all other aspects of this study as described below were followed through the termination announcement on November 25, 2024 and thereafter. Learnings from analyses of the sister study, PTI-125-07, were incorporated into this analysis plan.

This is a randomized, double-blind, placebo-controlled, parallel-group study of 76 weeks (19 months) duration in subjects with mild-to-moderate AD. The safety and efficacy of simufilam 50 and 100 mg tablets given twice daily will be evaluated with regard to the slowing of cognitive and

functional decline in AD subjects from 50 to 87 years of age.

In this Phase 3 clinical study, approximately 1083 participants with mild-to-moderate AD (361 per arm) will receive placebo or 50 mg tablets of simufilam or 100 mg tablets of simufilam, twice daily, for 76 weeks. Randomization (1:1:1) will be stratified by low or high mini-mental state exam (MMSE) (16-20 and 21-27).

Study participants 50-87 years of age will be selected for screening based on a diagnosis of AD consistent with Stages 4 or 5 on the Alzheimer's continuum (National Institute on Aging – Alzheimer's Association 2018). Participants must have MMSE $\geq$ 16 and $\leq$ 27, and a Clinical Dementia Rating Global Score (CDR-GS) of 0.5, 1 or 2. Finally, participants must have confirmed positron emission tomography (PET) or fluid biomarker evidence of AD pathophysiology prior to randomization.

Once participants have been satisfactorily screened for study participation, visits to the research clinic will occur on Study Day 1 and at Weeks 4, 16, 28, 40, 52, 64 and 76.

The co-primary endpoints include:

1. The 12-item Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog12) and
2. The Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL).

Secondary endpoints include the integrated Alzheimer's Disease Rating Scale (iADRS), Neuropsychiatric Inventory (NPI), MMSE, and the Clinical Dementia Rating Sum of Boxes (CDR-SB). A brief questionnaire assessing caregiver burden, the Zarit Burden Interview (ZBI), will be collected as an additional secondary endpoint.

Safety will be evaluated by adverse event monitoring, vital signs, clinical labs, and the Columbia Suicide Severity Rating Scale (C-SSRS) at every visit. Participants will undergo magnetic resonance imaging (MRI) during screening to ensure entry criteria are met (unless a recent MRI confirms entry criteria); however, 150 subjects (50 subjects per treatment group) will also undergo repeat MRI assessments at Weeks 40 and 76 to assess both long-term safety and drug impact on brain volume as noted above. Resting electrocardiograms (ECGs) will be conducted at baseline (Study Day 1) and Weeks 4, 40 and 76. A complete physical and neurological examination will be performed at screening, and brief examinations will be performed at all other visits. Weight will be measured during the Screening Period, at baseline (Study Day 1) and at all other visits.

A limited number of research sites will be invited to participate in one or more sub-studies to assess the impact of simufilam on anatomical and biomarker endpoints, including: change from baseline in CSF biomarkers (30 subjects/group), brain volume via MRI (50 subjects/group), and amyloid and tau PET (40 and 50 subjects/group, respectively). Participants in both PET sub-studies will be required to have an MRI during the screening period and provide plasma for a biomarker sub-study. Participants in the tau PET sub-study will also provide additional plasma for a PK exposure-response analysis. Change from baseline for these imaging and fluid biomarkers represent additional secondary endpoints.

The ninety subjects (30 per group) in the CSF sub-study will undergo lumbar puncture during the Screening Period and again at the Week 76 End-of-Treatment Visit to collect CSF biomarkers.

An independent DSMB will meet periodically to review participant safety assessments and determine if dosing may continue. A charter was developed with specific guidance for the DSMB.

There are no unblinded interim analyses of efficacy outcomes at any time prior to formal completion of the study and unblinding of the data.

2.2. Sample Size and Power

The sample size for this study was originally determined as follows.

Planned enrollment was approximately 1083 participants with mild-to-moderate AD. The sample size was determined by a power analysis of ADAS-Cog using data from a similar population over 76 weeks. This analysis determined that the comparison between an active arm and placebo requires group sizes of 289 to provide 90% power to detect a 45% difference from placebo at 76 weeks, based on the use of a two-sided test at the alpha = 0.05 significance level. The power calculation assumes a true mean change from baseline for placebo of 6.0 points and a standard deviation of 10.0 points. Assuming a drop-out of 20%, each treatment group should enroll approximately 361 participants.

Learnings from analyses of the sister study, and results from other development programs in AD led to change in the primary analysis population for this study to include in the primary analysis only those participants with >= 44 pg/ml P-tau181 at baseline, or other confirmation of amyloid pathology (e.g., amyloid PET). Based on results of study PTI-125-07, it is anticipated that the reduction in sample size will be offset by an increase in treatment effect such that the study will have at least as much power as originally planned.

2.3. Study Population

The study population is comprised of approximately 1083 male or female participants between the ages of 50 and 87 with mild-to-moderate AD. Participants are enrolled (randomized) from approximately 78 clinical sites in the U.S., Canada, Korea and Puerto Rico.

2.4. Treatments Administered

Participants were randomized in a 1:1:1 ratio to:

- simufilam 50 mg tablets BID, or
- simufilam 100 mg tablets BID, or
- placebo tablets BID.

The randomization was stratified by baseline low or high MMSE score (16-20 vs. 21-27).

2.5. Method of Assigning Participants to Treatment Groups

The randomization schedule was computer generated by an independent statistician and randomly allocated each treatment to randomization numbers. The randomization numbers were assigned sequentially through a central interactive response technology (IRT) system as participants entered the study. The randomization was stratified as described in section 2.4.

The randomization schedule will not be revealed to participants, clinical investigators, clinical staff, study monitors, blinded statistical personnel or Cassava Sciences until all participants have completed treatment and the database has been finalized and locked.

Participants who discontinue from the study or are terminated will not be replaced.

The IRT system will be used throughout the study for screening, randomization, study drug dispensation and management, and emergency unblinding. Individual participant treatment is automatically assigned by the IRT at baseline (Study Day 1) to participants who meet all entry criteria. The participant's randomization number is a unique number corresponding to the treatment allocated to the participant.

At each dosing visit, the site will access the IRT system and enter the necessary participant-specific information. For randomized participants, this information is used by the IRT system to dispense the correct dose and amount of study drug in a uniquely numbered bottle.

2.6. Blinding and Unblinding

All participants, investigators, and study personnel, including but not limited to sites, the Sponsor and Premier Research will be blinded to treatment assignment and receipt of study drug during the conduct of the study, through database lock. The treatment assignment will not be unblinded during the conduct of the study except in emergency situations where the identification of the study drug is required for the safety of an individual study participant. The investigator should make every effort to contact the medical monitor prior to individual participant unblinding or as soon as possible after unblinding without making the medical monitor aware of the treatment assignment.

If a treatment assignment is unblinded, the date and name of the person who was unblinded, and the reason for unblinding, are recorded in the appropriate source documents. The participant will be discontinued immediately from the study but will be followed up as required by standard medical practice. Unblinding will be managed via the IRT system.

Prior to unblinding, data that may functionally unblind personnel, including PK and biomarker results, will be handled with diligence. Any data that may unblind study personnel or the study team will be presented in blinded fashion only or withheld until after study unblinding.

The blinding of all study participant data will be maintained following the announcement on November 25, 2024, to discontinue this study until data lock.

2.7. Schedule of Events

The conduct of the study and different procedures performed from Screening Visit to End of Study Visit will be as per the visit schedule provided in Appendix A – Schedule of Activities.

2.8. Administration of Study Drug to Participants

Simufilam or placebo tablets will be supplied in 70-count bottles for a 4-week supply or 188-count bottles for a 12-week supply. Each bottle will contain 7 or 10 days of extra medication to accommodate scheduling flexibility with clinic visits. Each bottle is labeled with a unique double-blind identification (ID) number that is randomly assigned to a treatment. A computer-based clinical study management (i.e., IRT) system will specify the bottle ID number to be dispensed according to the participant's treatment randomization.

3. Study Objectives and Endpoints

3.1. Study Objectives

The general objectives of this study were originally stated as: to assess simufilam's safety and to

test the hypothesis that oral simufilam will slow the cognitive and functional decline in study participants with mild-to-moderate AD dementia. Secondary objectives include the assessment of simufilam's effect on neuropsychiatric symptoms and caregiver burden. A third objective is to investigate the effect of simufilam treatment on CSF, imaging, and plasma biomarkers.

The only change to this plan resulting from the early study termination is to focus on mild-to moderate AD in participants who are positive for P-tau181 at baseline or have other evidence of Amyloid pathology.

3.1.1. Primary Objective

The original primary objective was stated as: to assess simufilam's effect on the co-primary endpoints of ADAS-Cog12 and the ADCS-ADL, baseline to the end of double-blind treatment (Week 76). The early termination of the study did not change the primary objective.

3.1.2. Secondary Objectives

The original key secondary objectives are to assess simufilam's effect on changes from baseline to week 76 in the iADRS, NPI-10, MMSE, CDR-SB, and the ZBI. These are the secondary objectives for which multiplicity will be controlled. The early termination of the study did not change any of the secondary objectives.

Additional secondary objectives are to compare the co-primary and secondary endpoints in the subgroup of mild AD patients (stage 4 AD) with baseline MMSE scores of 21-27.

Additional secondary objectives that are not multiplicity controlled include the following:

- Mean change in the ADAS-Cog12 from baseline to Weeks 4, 16, 28, 40, 52, and 64
- Mean change in ADCS-ADL from baseline to Weeks 4, 16, 28, 40, 52, and 64.
- Mean change in the iADRS (range 0 – 139, lower score indicates greater impairment) from baseline to Weeks 4, 16, 28, 40, 52, and 64.
- Mean change in the NPI-10 (range 0 – 120, higher score indicates greater impairment) from baseline to Weeks 28 and 52
- Mean change in the MMSE (range 0 – 30, lower score indicates greater impairment) from the screening visit to Weeks 28 and 52.
- Mean change in the ZBI (range 0 – 88, higher score indicates greater caregiver burden) from baseline to Weeks 4, 16, 28, 40, 52 and 64.

3.1.3. Tertiary Objectives

To investigate the effect of simufilam treatment on mean changes from baseline in exploratory CSF, imaging, and plasma biomarkers.

3.2. Estimands

The primary estimand for the primary efficacy endpoints is defined as follows:

Population	The original population was specified as: Participants with mild-to-moderate AD dementia who meet the study's inclusion and exclusion criteria. The population of interest was changed after early termination, but while still

	blinded, to: Participants with mild-to-moderate AD dementia who meet the study's inclusion and exclusion criteria, and who have baseline P-tau181 ≥ 44 pg/ml or other evidence of amyloid pathology.
Treatments	Simufilam 100 mg twice daily or placebo (50mg twice daily is secondary).
Endpoints	ADAS-Cog12 (range 0 – 80, higher score indicates greater impairment) and ADCS-ADL (range 0 – 78, lower score indicates greater impairment).
Summary Measure	Difference between treatments in least squares (LS) mean change from baseline to Week 76.
Intercurrent Events	All deviations from the intended dosing regimens and use of concomitant medication will be handled using a treatment policy strategy. Early study discontinuation will be consistently accounted for using a hypothetical strategy to estimate what would have been observed if the participant had not discontinued.

The estimands for the multiplicity controlled secondary efficacy endpoint(s) are similar to the co-primary estimands. Each secondary estimand has the following components:

Population	The original population was specified as: Participants with mild-to-moderate AD dementia who meet the study's inclusion and exclusion criteria. The population of interest was changed after the early termination, but while still blinded, to: Participants with mild-to-moderate AD dementia who meet the study's inclusion and exclusion criteria, and who have baseline P-tau181 ≥ 44 pg/ml or other evidence of amyloid pathology.
Treatments	Simufilam 100 mg twice daily or placebo (50 mg twice daily is secondary)
Endpoints	iADRS, NPI-10, MMSE, CDR-SB, ZBI
Summary Measure	Difference between treatments in LS mean change from baseline to week 76
Intercurrent Events	All deviations from the intended dosing regimens and use of concomitant events medications will be handled using a treatment policy strategy. Early study discontinuation will be consistently accounted for using a hypothetical strategy to estimate what would have been observed if the participant had not discontinued.

In addition, secondary estimands include the primary and secondary endpoints assessed in the population of participants with stage 4 AD. Stage 4 (mild) is defined as participants with baseline MMSE 21-27. Stage 4 and 5 represent all randomized participants.

3.2.1. Safety Endpoints

The safety endpoints of this study include the following:

- Incidence of adverse events (AEs) including treatment-emergent, serious, related to study

drug, and leading to withdrawal along with AEs by severity and relationship to study drug

- Mean change in clinical laboratory values from baseline to Weeks 4, 16, 28, 40, 52, 64 and 76. Shifts in the normality of clinical laboratory values from baseline to Weeks 4, 16, 28, 40, 52, 64 and 76.
- Mean change in vital signs (blood pressure [supine], temperature, pulse rate) from baseline to Weeks 4, 16, 28, 40, 52, 64 and 76.
- Mean change in body weight from baseline to Weeks 4, 16, 28, 40, 52, 64 and 76.
- Shifts in physical exam (PE) findings from baseline to Weeks 4, 16, 28, 40, 52, 64 and 76.
- Shifts in neurological exam (NE) findings from baseline to Weeks 4, 16, 28, 40, 52, 64 and 76.
- Mean change in ECG parameters from baseline to Weeks 4, 40 and 76.
- Concomitant medications/treatments usage
- Shifts in the C-SSRS from baseline to Weeks 4, 16, 28, 40, 52, 64 and 76.

3.2.2. Pharmacokinetic Variable(s)

Plasma pharmacokinetic (PK) exposure response is part of a sub-study. A visit wise listing of Pharmacokinetic results will be provided. Summary will be presented in a separate report that will be appended to the CSR.

4. Statistical Analysis and Reporting

This SAP addresses the safety and efficacy objectives of the study and describes the statistical methods that Premier Research International LLC and Pentara Corporation will use to analyze the clinical data after the database has been finalized and locked.

4.1. Chain of Custody for Clinical Efficacy Data

Study sites collect clinical efficacy data from study participants using an electronic clinical outcome assessment (eCOA) device managed by Signant Health, an independent, outside data management and rater training vendor. Upon receipt of the data, Signant Health's clinical team conducts quality reviews of eCOA endpoints and provides feedback to study raters as appropriate. Signant Health also maintains the clinical efficacy database and transmits it periodically throughout the study to Premier Research to reconcile and package with additional data collected via electronic data capture (EDC). Premier Research also conducts quality reviews and may issue queries to study sites to reconcile any discrepancies. Upon completion of the study and once all visits have been deemed source data verified (SDV), Premier Research will analyze all study data related to safety and directly transmit study data to Pentara Corporation for analysis of all efficacy data. The pre-specified efficacy outcomes for this SAP will be executed by Pentara Corporation (an outside, independent biostatistical consulting firm headed by Suzanne Hendrix, PhD).

4.2. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and

graphical representations will use SAS (release 9.4 or higher). If the use of other software is required, the final clinical study report will specify the software that was used.

In general, summaries will be provided by study treatment group, unless otherwise noted. The column headings for the summaries will include the randomized treatment groups (Placebo BID, Simufilam 50 mg BID, Simufilam 100 mg BID), unless otherwise noted.

Continuous (quantitative) variable summaries will include the number of participants with non-missing values (n), mean, 2-sided 95% confidence interval (CI), standard deviation (SD) and/or standard error (SE) if applicable, median, and minimum and maximum values.

Categorical (qualitative) variable summaries will include the frequency and percentage of participants who are in the category for each possible value. In general, the denominator for the percentage calculation will be based upon the total number of participants in the study population for the treatment groups (or cohorts) unless otherwise specified.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) and bounds of CIs will be reported to 1 degree of precision more than the observed data and measures of spread (SD and SE) will be reported to 2 degrees of precision more than the observed data. Percentages will be presented to 1 decimal place.

Statistical testing and inference methods for safety and efficacy analyses are described below. Efficacy results will be considered statistically significant after consideration of the strategy for controlling the Type 1 error as described in Section 6.1.2 of this SAP. Nominal p-values may be computed for other efficacy analyses as a measure of the association between the endpoint and the treatment effect rather than formal tests of hypotheses. Unless otherwise stated, all statistical tests will be conducted at the alpha = 0.05 (two-sided) level, and a difference resulting in a p- value of $\leq$ 0.05 will be considered statistically significant. Corresponding 95% two-sided CIs will be presented for statistical tests.

All statistical comparisons will be based on LS means from the relevant contrasts in the mixed model for repeated measurements (MMRM) or analysis of covariance (ANCOVA).

The data from nominal/scheduled protocol clinic visits will be included in visit-based summary tables. Unscheduled assessments, if they occur, and the ET visit data will be mapped to scheduled assessments according to the visit windows defined in section 6.1.5 for all safety and efficacy analyses. See Section 6.1.4 and 6.1.5 of this SAP for more details.

4.3. Interim Analysis and Data Monitoring

No interim efficacy analyses or sample size re-estimations were planned to be conducted.

An external DSMB will be involved in the management of this study. The DSMB meeting will be held periodically for the duration of the study. The purpose of the DSMB is to review the progress of the study with special regard to safety and make recommendations to the Sponsor on how to handle any safety concerns that arise. Further details regarding the DSMB can be found in the DSMB charter which was finalized before the first meeting was scheduled.

5. Analysis Populations

The following analysis sets were originally planned for this study:

- **Intent-To-Treat (ITT) Analysis Set**: The ITT analysis set includes all randomized participants.
- **Intent-To-Treat mild (**ITT-mild**) Analysis Set:** The ITT-mild analysis set includes all randomized participants who have a baseline MMSE of 21-27.
- **Safety Analysis Set (SAF):** The SAF analysis set includes all participants who received at least one dose of study treatment. All safety analyses will be completed in the SAF analysis set and participants will be included in the group based on the treatment received.
- **PK sub-study Analysis Set:** The PK sub-study analysis set includes all participants who sign the PK consent and/or re-consent form and have at least one non-missing post baseline PK assessment available.
- **Sub-study analysis sets:** Analysis sets for the Plasma, CSF, and imaging biomarkers will each be created as subsets of the ITT dataset that includes only those participants from the ITT analysis set who were in the relevant sub-studies.
- **MRI sub-study Analysis Set:** The MRI sub-study analysis set includes all participants who sign the MRI consent and/or re-consent form and have at least one non-missing post baseline MRI assessment available.

After the early termination, the following analysis sets were added:

- **Modified intent-to-treat analysis set (mITT):** The mITT analysis set is a subset of the ITT analysis set that includes all randomized participants with baseline P-tau181 ≥44 pg/ml or other evidence of amyloid pathology (e.g., Amyloid PET).
- **Censored ITT analysis set (cITT):** Is the ITT analysis set with observations on and after the November 25, 2024, early termination announcement. Censored observations will be considered missing data.

Assignment of participants to analysis sets will be confirmed at a blinded data review meeting to be held before the study database is locked.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last observation recorded on or before the first dose of treatment will be used as the baseline observation for all calculations of change from baseline. In most cases, this will be the baseline visit (Day 1) pre-dose observation. In some cases, however, the baseline values may be obtained from the 60-day screening phase. For example, because MMSE is taken at screening but not at the baseline visit, the MMSE value obtained at screening will be used as the baseline value.

6.1.2. Adjustments for Covariates

Primary efficacy analyses will include as covariates the baseline value of the endpoint being analyzed and the MMSE baseline score, along with the interaction of these covariates with Visit. Investigative site (pooled, see section 6.1.6) will also be included as a categorical fixed effect. Covariates observed to be important in post-hoc analyses of the PTI-125-07 study will also be included in sensitivity analyses. See section 8.4 for further details.

6.1.3. Multiple Comparisons

The co-primary endpoints of ADAS-Cog12, and ADCS-ADL in the 100mg treatment arm will each be tested at p=0.05 using the mITT analysis set. Multiplicity among secondary endpoints for the 100 mg arm in the mITT analysis set will be controlled using a hierarchical, gatekeeping strategy. Secondary endpoints in the 100mg arm will be tested in the following order: iADRS, CDR-SB, ZBI, MMSE, and NPI-10. Testing will proceed in this order until the first non-significant p value ($p > 0.05$). The first endpoint with $p > 0.05$ and all subsequent endpoints in the order will be declared non-significant, and all endpoints preceding the first non-significant test will be declared significant. Endpoints that were significant in the 100mg arm will also be tested in the 50mg arm at $P = 0.05$.

For the set of significant endpoints in the 100 mg arm of the mITT analysis set, the corresponding endpoints in the mild subgroup (ITT-mild analysis set) will be tested. Testing for the mild cohort will proceed in the same order as for the secondary endpoints referenced above until the first non-significant p value. The first endpoint with $p > 0.05$ and all subsequent endpoints in the order will be declared non-significant, and all endpoints preceding the first non-significant test will be declared significant.

6.1.4. Handling of Dropouts or Missing Data

The original plan was that every attempt would be made to ensure participants remain in the study to completion and all data is collected as scheduled, the occurrence of missing data cannot be completely prevented. The early study termination creates more missing data than originally anticipated. However, the administrative censoring is independent of the treatments and outcomes in this study and is therefore considered missing completely at random. Therefore, the missing data from early stopping will not bias the MMRM results.

An incomplete start or stop date of an AE or a medication will be imputed as described in section 6.1.8.

Any participant who withdraws from the study will be considered to have missing data at all subsequent visits. The primary analytic approach for efficacy assumes missing at random (MAR) to estimate what would have been observed if the participant had not discontinued. A reference-based multiple imputation sensitivity analysis (copy reference) will be employed in which missing not at random is assumed such that after discontinuation, drug-treated participants will have placebo-like values imputed for their missing data.

If up to two individual items of the total 12 items for the ADAS-Cog12 (maximum score = 80) are missing for non-cognitive reasons, the total score will be imputed by multiplying the observed score (i.e. the score for the non-missing items) by a factor that includes the maximum scores for the missing item(s) as follows:

Imputed score = Observed score * (80/[80-maximum score for missing items]).

As an example, if the first item "Word Recall" (maximum score = 10) and the second item "Commands" (maximum score = 5) are missing, the observed score will be multiplied by the factor 80/(80-[10+5]) or 80/65 or 1.23. The imputed score will be rounded to the nearest integer. ADAS-Cog12 tests with more than two missing items will be considered missing scores.

Missing items on other assessments will not be imputed; such scores will be considered missing.

6.1.5. Analysis Visit Windows

All scheduled visits and associated variables for the treatment phase will be analyzed based on the study week to which they are assigned.

For the safety summaries and analyses, scheduled analysis visits will be windowed to the nearest scheduled visit and the unscheduled visits/assessments and early termination visits will be mapped to a scheduled visit using the following visit windows (Table 2.1 and Table 2.2). Visit windows will be assigned by splitting the periods between visits at the mid-point between the visits.

If both scheduled and unscheduled visits fall within the same visit window, scheduled visit will be used over unscheduled visits. If both scheduled and early termination visits fall within the same visit window, the data from the early termination visit will supersede.

If more than one unscheduled visit falls within the same visit window, the one closest to the target date will be used in the analysis. If equidistant, the earliest visit will be used.

If the analysis visit (for Unscheduled or ET assessments) falls on a visit window in which that specific assessment is not scheduled, then that assessment will not be used for analysis.

Table 2.1: Visit Windows for Safety (Except for ECG) Analysis

Scheduled Visit	Scheduled Visit Day (Target Day)	Window for Assignment of Analysis Visit (Study Days[1])
Week 4	Day 29	Day 2 – Day 71
Week 16	Day 113	Day 72 – Day 155
Week 28	Day 197	Day 156 – Day 239
Week 40	Day 281	Day 240 – Day 323
Week 52	Day 365	Day 324 – Day 407
Week 64	Day 449	Day 408 – Day 491
Week 76	Day 533	Day 492 – Day 575

[1]Study Day relative to the date of first dose of study drug.

Table 2.2: Visit Windows for Safety (ECG only) Analysis

Scheduled Visit	Scheduled Visit Day (Target Day)	Window for Assignment of Analysis Visit (Study Days[1])
Week 4	Day 29	Day 2 – Day 155
Week 40	Day 281	Day 156 – Day 407
Week 76	Day 533	Day 408 – Day 659

[1]Study Day relative to the date of first dose of study drug.

For the efficacy summaries and analyses, scheduled analysis visits are visits upon scheduled time points as specified in the Schedule of Time and Events. Scheduled analysis visits will be windowed

to the nearest scheduled visit. Assessments that fall within the same window will be averaged. There will be one valid value of assessment kept for each scheduled analysis visit in summary / analysis statistics.

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. All unscheduled visits will be included as collected in eCRF in listings.

6.1.6. Pooling of Sites

Sites with < 2 participants in any treatment arm at Week 76 will be pooled into a common site. All sites with ≥2 participants in both treatment arms at Week 76 will not be pooled.

6.1.7. Derived Variables and Conventions

Age: the age at baseline will be used.

Alzheimer's disease status

- MMSE = 21-27 (mild dementia)
- MMSE = 16-20 (moderate dementia)

Change from baseline = post-baseline value at timepoint – value at baseline

Time since diagnosis of AD (months) = (date of first dose – date of diagnosis) / 30.4375

Treatment duration (days) = (date of last dose of study drug – date of first dose of study drug) +1

Study Drug Exposure = treatment duration (days), that is the number of days a participant is on study drug will be calculated as the number of days from date of first dose to date of last dose plus 1.

Study Drug Compliance (%) = 100 x Total number of tablets taken / Total number of expected tablets. That is, 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 participant's participation in the study.

Study drug compliance will not be calculated for participants whose date of last study drug is unknown.

Total Dose (mg) = $\sum$ [Number of doses taken$_i$ x Dose received (mg)$_i$]

where,

i = 1 to k, (k = number of time periods participant is receiving a constant dose)

Average Daily Dose (mg/day) = Total Dose (mg) / Treatment Duration (days)

Dose variables (dose, total dose, and average daily dose) not calculated for placebo participants.

The iADRS for this trial is a composite endpoint that combines scores from the 12-item AD Assessment Scale-Cognitive subscale (ADAS-Cog12) and the AD Cooperative Study - instrumental Activities of Daily Living (ADCS-iADL). The ADCS-iADL is defined as items 6a and 7-23 of the ADCS-ADL.

iADRS score = [-1(ADAS-Cog12) + 80] + ADCS-iADL

6.1.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings or Clinical Data Interchange Standards Consortium (CDISC) datasets. Analysis results will be presented and summarized in either tables and/or figures. Data not participant to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings.

All p-values will be displayed in four decimals and rounded using standard scientific notation (e.g., 0.XXXX). If a *p-value* less than 0.0001 occurs, it will be shown in tables as < 0.0001.

The version 24.0 of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to classify all AEs by system organ class (SOC) and preferred term (PT).

Prior and concomitant medications will be classified using Anatomical Therapeutic Chemical class (ATC level 2) and preferred term (ATC level 4) from World Health Organization Drug Dictionary (WHO-DD), WHODrug Global B3 version March2021.

Medications that start before the first dose of study drug are considered prior medications whether or not they were stopped prior to the first dose of study drug. Any medication continuing or starting on or after the first dose of study drug will be considered as concomitant. If a medication starts prior to the first dose of study drug and continues after the first dose of study drug, the medication will be considered as both prior and concomitant.

Adverse events or medications with entirely missing start dates will be classified as treatment-emergent or concomitant, as appropriate.

For partial AE or medication start dates: (a) if only the day is missing, and the month and year match the first dose date and the end date is on or after the first dose date, or AE/medication is ongoing, then the date is assigned the first dose date thus the event/medication will be considered as treatment-emergent/concomitant; if the month and/or year do not match the first dose date or the end date is prior to the first dose date, then the day is assigned the first day of the month (01); (b) if month or the day and month are missing, and the year matches the first dose date and the end date is on or after the first dose date, or AE/medication is ongoing, then the date is assigned the first dose date; if the year does not match the first dose date or the end date is prior to the first dose date, then the day/month are assigned the first day of the year (01JAN).

For partial end dates: (a) if only the day is missing, then the day is assigned the last day of the month; (b) if both day and month are missing, they are assigned the last day of the year (31DEC).

For analysis purposes, repeat laboratory results will not be used unless the original value is indicated as missing or invalid. In such cases, the first non-missing repeat value will be used for data analysis. The international system of units (SI) will be used in reporting all laboratory values.

Participants will be analyzed by the treatment received for all safety and tolerability assessments.

Participants are stratified through the IRT system based upon MMSE score entered. Once an MMSE score is entered, that participant is randomized to either high MMSE (21-27) or low MMSE (16-20) strata. At study start, it was decided to stratify participants in this manner so there would be a balance in the number of participants on placebo vs active drug (and within treatment arms) within each stratum. The stratification of the participants does not impact their probability of being

assigned to different treatment arms. Once randomized through IRT, the MMSE score and the stratification assigned cannot be changed.

For instances where the MMSE score was incorrectly entered into IRT, the MMSE score given by the vendor will be used to calculate the strata for safety and efficacy analyses if there are any subgroup analyses.

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

A treatment related AE is any AE with a relationship to the study drug of *"Possibly Related" or "Probably Related" or "Reasonable Possibility".*

If partial dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows: if just day is missing then the day assigned is the first day of the month or the date of first dose (if in the same month), whichever is later; if just month is missing then the month assigned is the month of the first dose, unless that results in a date before the first dose in which case the month after the first dose is used; and if both month and day are missing then the month assigned is the month of the first dose and the day assigned is either the first day of the month or the first dose date, whichever is later.

If partial times occur, the convention is as follows: if the missing time occurs on the day of the first dose and both the hour and minute are missing then the time assigned is the time of the first dose, otherwise if both the hour and minute are missing and the date is not the date of first dose the time assigned is 12:00; if the date is the same as the date of the first dose and only hour is missing the hour assigned is 12 or the hour of first dose, whichever is later, and if the date is the same as the date of first dose and only the minute is missing the minute assigned is 30 or the minute of first dose, whichever is later. Otherwise, the hour assigned is 12 if the hour is missing and the date is not the same as the date of first dose and the minute assigned is 30 is the date is not the same as the date of first dose.

These conventions will be applied only to adverse event onset dates and times with the following precaution: if the missing date and time reflect the date and time of onset of an adverse event, the modified date and time will be constructed to match the first documented date/time post drug administration while preserving the order in which the AE was reported in the CRF.

7. Study Participants and Demographics

Participant disposition, demographics and other baseline characteristics, prior medications, and study drug exposure and compliance will be summarized by randomized treatment group and overall, using the ITT analysis set, unless otherwise specified below in each section.

7.1. Disposition of Participants and Withdrawals

Since this is a long-term study in a patient population that is elderly with multiple possible comorbidities, some participant withdrawal will occur. Efforts will be taken to obtain information on participants who are initially categorized as lost to follow-up. From the randomized population, the disposition of participants withdrawing from each treatment arm will be summarized and compared.

Participant disposition will include tabulations of the number of overall participants who screen failed for blinded treatment period. The following will be summarized by randomized treatment group and overall:

- Number of participants who enrolled/randomized,
- Number and percentage of participants in each analysis set,
- Number and percentage of participants who completed the study, and
- Number and percentage of participants who discontinued from the study, including the reason for study discontinuation.

The percentage of participants will be based on the mITT analysis set. All disposition results will be presented in a data listing.

7.2. Protocol Violations and Deviations

The severity (important/non-important) will be classified using the following definitions as per Premier Research standard operating procedures (SOPs). A protocol deviation is any noncompliance with the clinical trial protocol or International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (R2) Good Clinical Practice (GCP) requirements.

Protocol deviations will be tracked, recorded, and reviewed prior to database lock, following the Protocol Deviation Guidance Plan for this study.

Potentially important deviations will be reviewed by the Sponsor and Premier to determine the final classification. Protocol deviations which are deemed to be “Important” and “Non-Evaluable” (i.e., a deviation that has a potential impact on the efficacy analysis), will be classified into a separate category.

The protocol deviation categories will be:

- Inclusion Criteria
- Exclusion Criteria
- Study Drug
- Assessment – Safety
- Assessment – Efficacy
- Lab/Endpoint Data
- Visit Window
- Informed Consent
- Prohibited Concomitant Medication
- Overdose/Misuse
- Other

The number and proportion of participants with important protocol violations/deviations will be tabulated by category/type and treatment group in the safety analysis set. These protocol violations/deviations will also be presented in a participant listing by randomized treatment.

7.3. Demographics and Other Baseline Characteristics

All participant demographics and other baseline characteristics will be summarized by randomized treatment group using the ITT analysis set. Demographic and other baseline characteristics will also be summarized for the safety analysis set if it is different from the ITT analysis set.

Demographic and baseline characteristics [age, sex (including child-bearing potential for women), methods of contraception, race, ethnicity, weight, height, body mass index (BMI), and education level] will be summarized using the descriptive statistics. Height and weight will be calculated at screening and then the BMI will be calculated at screening.

Additionally, baseline characteristics including AD family history, Covid-19 infection and vaccination history results, and Apolipoprotein E (ApoE) genotyping will be summarized.

The number and percent of participants reporting medical history, grouped by MedDRA system organ class and preferred term, will be tabulated by randomized treatment group. All medical history data will be presented in a data listing.

Prior medications will be summarized descriptively by treatment group using the number and percentage of participants by Anatomical Therapeutic Chemical class (ATC level 2) and preferred term (ATC level 4). All “Cognitive enhancers” defined by verbatim terms: donepezil (Aricept, Adlarity), galantamine (Razadyne, Reminyl), rivastigmine (Exelon) and memantine (Namenda, Ebixa, Nemdatine) will be summarized separately. All prior medication data will be listed. The cognitive enhancers will be flagged in the prior medication listing.

For the continuous variables, the number of non-missing values and the mean, standard deviation, minimum, median, and maximum will be tabulated.

For the categorical variables, the count and percentage of each value will be tabulated.

7.4. Exposure and Compliance

Study drug exposure and compliance data will be collected in the case report form (CRF).

Study drug exposure data will be summarized as treatment duration (days), study drug exposure (days), and average daily dose (mg/day) by treatment received and overall.

Study drug compliance data will be summarized as total number of planned doses (tablets), total number of doses (tablets) taken, and compliance (%) by treatment received and visit.

Compliance will be summarized as a continuous outcome using mean, SD, median, min, and max, and as a categorical variable. For the categorical analysis, a participant 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.

All study drug administration, accountability and exposure data will be listed.

8. Efficacy Analysis

8.1. Co-Primary Efficacy Analysis

Visit wise mean changes from baseline will be analyzed in the mITT analysis set using a restricted maximum likelihood (REML)-based repeated measures approach (MMRM). The MMRM analysis assumes a missing at random (MAR) missing-data mechanism, meaning that drop out is related to observed outcomes of the dependent variable and covariates, but not to the unobserved outcomes. The analysis will include the categorical, fixed effects of treatment group (3 levels), visit (7 levels), and pooled site, along with the continuous, fixed covariates 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-participant 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, heterogeneous compound symmetric, and compound symmetric. If one of the structures other than unstructured is used, variance of the Maximum Likelihood Estimator (MLE) will be based on the Sandwich Estimator (empirical option in PROC MIXED statement). If none of the structures yield convergence, site will be removed from the model and the sequence of covariance structures will be refit as described above. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Significance tests for the between-treatment group differences will use a two-sided 0.05 level, with the co-primary analyses using the mITT analysis set.

8.1.1. Sensitivity Analyses of the Primary Efficacy Endpoint

The co-primary analyses will also be applied to the ITT, cITT, and ITT-mild analysis sets.

In addition, a missing not at random (MNAR)-based copy reference approach will be used as a sensitivity analysis to assess robustness of inferences on the co-primary analyses, (mITT analysis set) to departures from MAR. Mean changes from baseline in the co-primary endpoints will be analyzed based on data observed while the participants remain on study as well as data imputed using multiple imputation for time points at which no value is observed.

Imputation of values in the reference (placebo) arm will assume MAR. Imputation of values in the active arm will be based on the imputation model for the placebo group, thereby imputing placebo-like values for drug group dropouts. This approach assumes any benefit from the active treatment diminishes over time in accordance with the correlations between repeated measurements.

Intermittent (non-monotone) missing data will be imputed first based on MCMC. An example code fragment is included below. YOBS1-7 are the seven postbaseline values of the endpoint being imputed.

```
PROC MI DATA = XXX OUT = YYY_MIOUT NIMPUTE=200 SEED=123;
   BY TRT;
   MCMC IMPUTE = MONOTONE;
   VAR BASELINE MMSE_BASELINE YOBS1 YOBS2 YOBS3 YOBS4 YOBS5 YONS6 YOBS7;
RUN;
```

The remaining monotone missing data for all participants who discontinue study prematurely will be imputed using a sequential regression multiple imputation model based on data from the

reference arm (placebo, denoted as trt 1 in the code below) only. Missing values in the placebo and two active arms will be imputed from the imputation model developed from the placebo arm. No rounding or range restrictions will be applied to imputed continuous values.

Example code to implement this analysis is listed below.

```
PROC MI DATA=YYY_MIOUT SEED=1214 OUT=YYY_MIOUT2 round=1 NIMPUTE=200;
        CLASS TRT;
        MONOTONE METHOD=REG;
        VAR  BASELINE MMSE BASELINE YOBS1 YOBS2 YOBS3 YOBS4 YOBS5;
        MNAR MODEL (Y1 / modelobs=(trt'1'));
        MNAR MODEL (Y2 / modelobs=(trt'1'));
        MNAR MODEL (Y3 / modelobs=(trt'1'));
        MNAR MODEL (Y4 / modelobs=(trt'1'));
        MNAR MODEL (Y5 / modelobs=(trt'1'));
        MNAR MODEL (Y6 / modelobs=(trt'1'));
        MNAR MODEL (Y7 / modelobs=(trt'1'));
Run;
```

The primary MMRM model will be applied to the multiply imputed data sets with results combined using Rubin's rules as implemented in PROC MI Analyze.

Another sensitivity analysis will employ a hypothetical strategy rather than the treatment policy strategy for changes in concomitant medications that are known to have a cognitive enhancing effect. This analysis will be identical to the primary analysis except that data will be censored after a participant has a post-baseline change in dose or a post-baseline initiation of a cognitive enhancing treatment. By deleting the post-change in concomitant medication data, the MMRM analysis will estimate what would be expected if the participants had not added or initiated cognitive enhancing medication.

To assess sensitivity of inferences to handling of the intercurrent event of death, the following approach will be used. Missing data resulting from patient death will be imputed using the worst observed result at each respective visit. The primary analysis as described above will be applied to this data set.

8.2. Secondary Efficacy Analysis

The following secondary endpoints will be analyzed in the mITT, ITT, cITT, and ITT-mild analysis sets: iADRS, MMSE, NPI-10, and ZBI. The MMRM model as described for the primary analyses will be used, with the exception for MMSE where the baseline value for the endpoint being analyzed is the MMSE baseline; therefore, the model for MMSE will include the categorical fixed effects of treatment group, Visit, and pooled site, along with the continuous, fixed covariate of baseline MMSE score and the interactions of treatment group and baseline MMSE with Visit.

The CDR-SB is collected only at Screening and Week 76 or ET/ED. Therefore, the CDR-SB will be analyzed using ANCOVA with a model that includes treatment group, pooled site, and baseline MMSE.

8.3. Tertiary/Exploratory Efficacy Analysis

Plasma and imaging biomarkers that are collected repeatedly post-baseline will be analyzed with

the MMRM analysis as described above.

CSF and imaging biomarkers that are collected only at screening/baseline and Week 76 ET/ED will be analyzed using ANCOVA with a model that includes treatment group, pooled site, and baseline MMSE.

8.4. Subgroup Analyses of Efficacy Variables

The co-primary endpoints and iADRS will be analyzed in a subset of the mITT analysis set, termed the "amnestic subset", in which the following additional restrictions are applied: baseline CDR global score ≥1 and baseline score on the CDR memory domain ≥ 1.

The co-primary endpoints and iADRS will be analyzed in the ITT analysis set by baseline severity, with subgroups defined as screening MMSE ≥ 21 and ≤ 27 versus MMSE < 21. An additional subgroup analysis for the co-primary endpoints and the iADRS will use screening MMSE ≥ 20 and ≤ 27 versus MMSE < 20. For these analyses, an MMRM model as previously described will be used, except that the model will have additional fixed effects for subgroup and its two-way interactions with treatment and Visit, and the 3-way subgroup-by-treatment-by-Visit interaction; and, baseline scores for the endpoint being analyzed and baseline MMSE and their interactions with Visit will be removed from the model due to their possible confounding with subgroup. Specifically, the analysis will include the categorical, fixed effects of treatment group, subgroup, pooled site, and Visit, along with the two-way interactions of treatment group with Visit and subgroup with Visit, and the three-way treatment group, subgroup, Visit interaction.

Similar models will be used to analyze subgroups by age (defined as < 65, 65-74 or ≥ 75), sex (defined as male or female), ethnicity (categories defined per FDA Guidance), race, ApoE4 genotype (defined as APOE4 non-carrier, carrier or homozygous) and medication use (cognitive enhancers, defined as yes or no).

There will be two additional subgroup analyses for the NPI-10. The first will include participants with a baseline NPI-10 score ≥ 2. The second will analyze the agitation/aggression domain scores in participants with a non-zero baseline score in that domain.

Note that there will be two sets of results for the mild subgroup. In section 8.2 the mild subgroup analyses are conducted by applying the primary analysis model to the ITT-mild analysis set. Those analyses are the primary means of drawing inference for the mild subgroup. The subgroup analyses described here for the mild / moderate subgroups are the primary means of drawing inference for differential efficacy between the subgroups. The analyses specified in section 8.2 are the primary means of understanding efficacy within the mild subgroup because that approach allows for including the same model as other secondary and primary endpoints.

In addition, subgroup analyses will be conducted by baseline severity and baseline plasma P-tau181 level. Baseline severity will be defined by iADRS, a composite of ADAS-Cog12 and ADCS-ADL. Each participant will be categorized as high, medium, or low baseline severity by dividing the baseline iADRS scores into tertiles. Baseline P-tau181 will be defined as high or low based on a median split. The 4-way interaction between baseline composite severity category, baseline P-tau category, Visit, and Treatment will be fit in an MMRM model to assess the changes over time by treatment within the six categories defined by the baseline composite and baseline P-tau categories. Within-patient errors will be modeled as described for the primary analysis.

8.5. Responder Analyses

A responder analysis will report the number and percentage of participants in each treatment group who remain stable or show improved scores on the co-primary endpoints (analyzed separately), baseline to week 76. These analyses will be conducted for all participants, and for the mild and moderate subgroups.

A second responder analysis for the NPI-10 will report the number and percentage of participants in each treatment group with a score of 0 at baseline and these numbers and percentages with a score of 0 again at week 76. This analysis will also be conducted for mild and moderate subgroups.

The significance of the difference between treatments in response rates will be assessed using the Cochran-Mantel-Haenszel (CMH) test in all participants, stratified by mild / moderate disease status; and the difference in response rates within disease subgroups will be assessed using the CMH test stratified by ApoE4 carrier status.

8.6. Disease Progression Analyses

A progression analysis will report the number and percentage of participants in each treatment group who entered the study with mild disease at baseline (MMSE 21-27) and who then progress to moderate or to more severe disease (MMSE 16-20 and MMSE <16, respectively) by week 76.

A second progression analysis will report the number and percentage of participants in each treatment group who entered the study with moderate disease at baseline (MMSE 16-20) and who then progressed to more severe disease (MMSE <16) by week 76.

The significance of the difference between treatments in the rate of disease progression will be assessed using the CMH test in all participants, stratified by mild / moderate disease status; and the difference in progression rate within disease subgroups will be assessed using the CMH test stratified by ApoE4 carrier status.

8.7. Time-Based Analyses

Mean changes from baseline in the co-primary endpoints will be described in terms of time savings. The mean change from baseline at Week 76 in the active arm will be mapped back to the time point at which the mean change in the placebo arm was equal to the active arm change at Week 76. A cubic spline interpolation will be used for precise time mapping between visits. Similar mappings will be done for the mean changes ± the SE of the mean changes. If a time mapping is outside the range spanned by the reference trajectory (e.g., mapping standard errors near the beginning or end of follow-up), time will be mapped off the range spanned by the reference trajectory via the line connecting the first visit for change from baseline (0, 0) for change from baseline measures and last visit measures. This time component test will be done based on all participants and for the mild and moderate subgroups.

8.8. Pooling With Other Studies

Data from Protocol PTI-125-06 will be pooled with data from Protocol PTI-125-07. These pooled analyses will include data from weeks 0 – 52 from Protocol PTI-125-06 to match the duration of Protocol PTI-125-07. Objectives and estimands for the pooled data will mirror those in Protocol

PTI-125-07. Analyses will also be similar but will include an additional categorical fixed effect of study. These pooled data will be analyzed using the co-primary and multiplicity adjusted secondary endpoints and by the subgroups defined by baseline composite severity / baseline P-tau categories.

Additional analyses may be applied to the pooled data based on the findings of the PTI-125-06 study.

9. Safety and Tolerability Analysis

All safety analyses will be performed on the safety analysis set.

Safety measures including AEs, clinical laboratory values, physical examination findings, neurologic examination findings, vital signs, ECGs, and concomitant medication usage will be summarized descriptively. No inferential statistical tests will be performed, unless otherwise specified. For quantitative variables, descriptive statistics including number of observations, mean, median, standard deviation, minimum, and maximum will be presented for observed and change from baseline values at each study visit. Qualitative variables will be summarized using counts and percentages.

For all safety and tolerability analyses, participants will be analyzed by the actual treatment and dose received and, if applicable, overall.

All safety and tolerability data will be presented in participant listings.

9.1. Adverse Events

An AE is any undesirable event that occurs to a participant during a study, whether that event is considered related to Study Drug.

All summaries of AEs will be based on treatment-emergent adverse events (TEAEs) unless specified otherwise.

An adverse event is considered a TEAE if:

- The adverse event first occurred on or after the date of the first dose of study drug; or
- The adverse event was present before the date of the first dose of study drug, but it increased in severity or became serious on or after the date of the first dose of study drug.

9.1.1. Severity of Adverse Events

The severity of each AE should be characterized and then classified into one of three clearly defined categories as follows:

- Mild
- Moderate
- Severe

These three categories are based on the Investigator's clinical judgment, which in turn depends on consideration of various factors such as the participant's report and the physician's observations.

The missing severity of an AE will be imputed to “severe”.

9.1.2. Relationship to Study Drug

The relationship of each AE to the Study Drug will be based on the Investigator's assessment as to whether there is a reasonable possibility the AE was caused by the Study Drug.

The causal relationship between an AE and the study drug will be categorized as two cases in the CRFs as follows:

Case 1: If AE started while participant was consented under protocol v 2.0, then the categories will be

- Unlikely Related,
- Possibly Related, and
- Probably Related.

The missing relationship to study drug of an AE will be imputed to "Probably Related".

Treatment-related TEAEs are defined as the TEAEs with relationship to study drug is "Possibly Related" or "Probably Related".

Case 2: If AE started while participant was consented under protocol v 3.0 and/or above, then the categories will be

- Not Related, and
- Reasonable Possibility.

The missing relationship to study drug of an AE will be imputed to "Reasonable Possibility".

Treatment-related TEAEs are defined as the TEAEs with relationship to study drug is "Reasonable Possibility."

For the analysis purposes (regardless of protocol amendment version), treatment-related TEAEs are defined as the TEAEs with relationship to study drug is "Possibly Related" or "Probably Related" or "Reasonable Possibility."

9.1.3. Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) includes (but is not limited to) an experience occurring at any dose that results in any of the following outcomes:

- Death,
- Life-threatening,
- In-patient hospitalization,
- A persistent or significant disability/incapacity,
- A congenital anomaly/birth defect, and
- Other medically important event

The number and proportion of participants who experience the event according to MedDRA system organ class (SOC) and preferred term (PT) will be presented by treatment group. TEAEs

will be further summarized, individually, by maximum severity and relationship to study drug. Adverse events related to study drug, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized.

An overall summary of TEAEs will be provided by treatment. This summary will present number and percentage of participants with TEAEs per the following classifications:

- Participants with any TEAEs
- Participants with Treatment-Emergent Drug-Related AEs
- Participants with Treatment-Emergent AEs by Maximum Severity as Mild, Moderate, and Severe.
- Participants with TEAE leading to discontinuation from study
- Participants with Treatment-Emergent SAEs
- Participants with Treatment-Emergent SAEs leading to discontinuation from study
- Participants with Treatment-Emergent SAEs resulting in death

The following summary tables for TEAEs will be presented:

- Number and percent of participants reporting treatment-emergent AEs, grouped by MedDRA system organ class and preferred term
- Number and percent of participants reporting treatment-emergent drug-related AEs, grouped by MedDRA system organ class, and preferred term
- Number and percent of participants reporting treatment-emergent AEs, grouped by MedDRA system organ class, preferred term, and maximum severity
- Number and percent of participants reporting treatment-emergent SAEs will be tabulated by system organ class and preferred term and presented by treatment.
- Number and percent of participants reporting treatment-emergent AEs leading to study discontinuation, grouped by MedDRA system organ class and preferred term

For the summary tables above, the SOC terms and PTs will be presented in decreasing order of the total number of participants (frequency) who experienced each AE. System organ class terms and PTs with the same frequency will be presented alphabetically. In the case of multiple occurrences of the same TEAE within the same participant, each participant will only be counted once for each preferred term.

The following data listings for AEs will be provided for each participant by displaying the events captured on the CRF:

- All AEs,
- All serious AEs,
- All AEs leading to study discontinuation, and
- All AEs leading to Death.

In the AE data listings, all AEs will be displayed. AEs that are not treatment-emergent will be flagged in the AE listings.

9.2. Clinical Laboratory Evaluations

The following clinical laboratory tests will be performed during the Screening Period, Baseline (Study Day 1) pre-dose, and at all follow-up visits (Week 4, Week 16, Week 28, Week 40, Week 52, Week 64, and Week 76/ET/ED).

Table 3: Protocol-Required Safety Laboratory Tests

Hematology		
Erythrocytes (RBC)	Eosinophils (EOS)	Leukocytes (WBC)
Hemoglobin (HGB)	Lymphocytes (LYM)	Eosinophils/Leukocytes (EOSLE)
Hematocrit (HCT)	Monocytes (MONO)	Lymphocytes/Leukocytes (LYMLE
Platelets (PLAT)	Neutrophils (NEUT)	Monocytes/Leukocytes (MONOLE)
Basophils (BASO)	Basophils/Leukocytes (BASOLE)	Neutrophils/Leukocytes (NEUTLE)
Serum Chemistry		
Alanine aminotransferase (ALT)	Calcium (CA)	Phosphate (PHOS)
Albumin (ALB)	Chloride (CL)	Potassium (K)
Alkaline phosphatase (ALP)	Gamma-glutamyl transferase (GGT)	Protein (PROT)
Aspartate aminotransferase (AST)	Globulin (GLOBUL)	Sodium (SODIUM)
Bicarbonate (BICARB)	Glucose (GLUC)	Urea Nitrogen (UREAN)
Bilirubin (BILI)	Creatinine (CREAT)	Urate (URATE)
	Lactate dehydrogenase (LDH)	
Urinalysis*		
Color (COLOR)	Leukocyte esterase (LEUKASE)	Protein (PROT)
Glucose (GLUC)	Nitrite (NITRITE)	Specific gravity (SPGRAV)
Ketones (KETONES)	pH (PH)	Occult Blood (OCCBLD)

* A “reflex” microscopic examination will be performed if protein, occult blood, nitrites, or leukocyte esterase is present on the basic analysis.

Screening Period: During the Screening Period only, bloods will be drawn for TSH, free T4, Vitamin B12, HepBsAg, HCV-Ab, HbA1C (diabetic participants only) and plasma P-tau181 (Note – plasma collection for P-tau181 not required if participant has documented evidence of AD pathophysiology prior to screening). Urine to screen for drugs of abuse (amphetamines, cocaine, opiates and phencyclidine) will also be collected during the Screening Period.

All hematology, chemistry, and urinalysis laboratory results will be presented in SI units, if available. Only laboratory parameters in the Table 3, will be tabulated.

The observed values and changes from baseline of all quantitative safety laboratory results for clinical chemistry, hematology, and urinalysis (only for pH and Specific Gravity results) will be summarized using descriptive statistics showing the number of observations (n), mean (SD), median, minimum, and maximum value. A separate summary table with the number and percentage of participants for each categorical urinalysis parameter (glucose, protein, occult blood, ketone, nitrite, and leukocyte esterase) will be provided.

Baseline values for all clinical chemistry, hematology, and urinalysis parameters will be categorized as being below the normal range (Low), within the normal range (Normal), and above the normal range (High). Shift from baseline tables will present the number and percentage of participants who have observations that are Normal, Low, or High when such range characterizations are available. Shift tables will be presented for values shifting from Baseline (Study Day 1) to the Week 76/ET/ED.

Listings of all observed chemistry, hematology, and urinalysis laboratory data will be provided. Laboratory results outside the normal range will be flagged. The abnormal values will be flagged with 'L' (low) for values below the lower limit of the laboratory's normal range or 'H' (high) for values above the upper limit of the laboratory's normal range. Abnormal values will be graded as not clinically significant (NCS) or clinically significant (CS).

Abnormal results from the microscopic examination will be listed. All other laboratory assessments will only be listed.

9.2.1. Stopping Criteria

Potential discontinuation of study drug for abnormal liver function tests should be considered if the study participant meets one or more of the following liver chemistry threshold stopping criteria:

- ALT or AST ≥ 4x ULN;
- ALT or AST ≥ 3x ULN and total bilirubin ≥ 2x ULN;
- ALT or AST ≥ 3x ULN if associated with the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia;

or

- ALP elevations, if deemed of liver origin and drug-related as follows:
    - ALP > 3x ULN;
    - ALP > 2.5x ULN and total bilirubin > 2x ULN; or
    - ALP > 2.5x ULN if associated with the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia,

  where ULN = Upper Limit of Normal.

Study drug should be discontinued if a participant: (1) positively affirms suicidal ideation in response to questions number 4 or 5 in the suicidal ideation section of the C-SSRS, or (2) reports any suicidal behavior or non-suicidal self-injurious behavior since their last visit in response to the C-SSRS Suicidal Behavior questions.

Bodyweight loss (compared to weight at Baseline Visit [Study Day 1]) of ≥ 2 kg resulting in a BMI < 18.5 is an additional stopping criterion.

Individual results of stopping criteria will be listed and summarized by presenting the number and percentage of participants who meet at least one post-dose stopping criteria.

9.3. Vital Signs

Descriptive summaries of observed values and changes from baseline will be presented for systolic

blood pressure, diastolic blood pressure, heart rate, and temperature which will be measured at the following visits.

Screening Period, Baseline (Study Day 1), Week 4, Week 16, Week 28, Week 40, Week 52, Week 64 and Week 76/ET/ED.

Body weight will be summarized descriptively in the tabulations for the visits at which it will be measured.

Body Mass Index (BMI): Baseline BMI results will be used from vital sign page in EDC and post baseline BMI results will be derived using post baseline body weights at each visit and screening height. A visit wise descriptive summary and change from baseline analysis of BMI will be provided.

Formula for BMI = weight in kg/ (height in metre)^2.

All vital signs results will be listed.

9.4. Standard 12-lead ECG

12-lead ECGs will be performed at the following visits:

Screening Period, Baseline (Study Day 1), Week 4, Week 40, and Week 76/ET/ED.

12-lead ECG readings will be obtained using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS interval, RR interval, QT interval, QTcB interval (corrected QT according to Bazett), and QTcF interval (corrected QT according to Fridericia). All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

12-lead ECGs will be performed in triplicate at Baseline (Study Day 1) and thus the triplicates will be averaged for the summaries.

The ECG results will be interpreted as ‘Normal’, and ‘Abnormal, Not Clinically Significant (NCS)’, and ‘Abnormal, Clinically Significant (CS)’.

The overall assessment by treatment group will be summarized at each timepoint using number and percent of participants.

For Heart Rate (beats/min), PR interval (msec), RR Interval (msec), QRS Interval (msec), QT Interval (msec), QTcF (msec), QTcB (msec), the observed and change from baseline data will be descriptively summarized by treatment group showing the number of observations (n), mean, SD, median, minimum, and maximum value.

The number and percentage of participants having observed QT, QTcB and QTcF values that satisfy the following conditions will be summarized:

- $\leq$ 450 msec
- > 450 to $\leq$ 500 msec
- > 500 msec

The number and percentage of participants having change from baseline QT, QTcB and QTcF values that satisfy the following conditions will be presented:

- ≤ 0 msec
- > 0 to ≤ 30 msec
- > 30 to ≤ 60 msec
- > 60 msec

All ECG findings will be listed.

9.5. Further Safety Evaluations

9.5.1. Physical Examinations

A **complete** physical examination will include the body systems: Skin, Head, Ears, Eyes, Nose, Throat, Neck/Thyroid, Lymph Nodes, Cardiovascular, Respiratory, Abdomen, Musculoskeletal, Extremities, and Other; and it will be performed at the Screening visit only. All participants with 'Normal', 'Abnormal, Not Clinically Significant (NCS)', and 'Abnormal, Clinically Significant (CS)' physical exam (complete) findings will only be listed.

A **brief** physical examination will include the body systems: general appearance, Cardiovascular, Respiratory, Abdomen, and Other; and it will be performed at the following visits:

Baseline (Study Day 1), Week 4, Week 16, Week 28, Week 40, Week 52, Week 64 and Week 76/ET/ED.

The number and percentage of participants with 'Normal', 'Abnormal, Not Clinically Significant (NCS)', and 'Abnormal, Clinically Significant (CS)' physical exam (brief) findings will be summarized by study visits.

All brief physical examination findings will be listed.

9.5.2. Neurologic Examinations

A complete neurologic examination will be performed at the Screening visit only. All complete neurologic examination findings will only be listed.

A brief neurologic examination will include the exam categories; cranial nerves [II-XII], tone, power, deep tendon reflexes, coordination, and gait; and it will be performed at the following visits: Baseline (Study Day 1), Week 4, Week 16, Week 28, Week 40, Week 52, Week 64 and Week 76/ET/ED.

The number and percentage of participants with 'normal', 'Abnormal', and 'Not Done' neurologic exam (brief) findings will be summarized by study visits.

All brief neurologic examination findings will be listed.

9.6. Concomitant Medications

Concomitant medications will be summarized descriptively by treatment group using the number and percentage of participants by Anatomical Therapeutic Chemical class (ATC level 2) and preferred term (ATC level 4).

All "Cognitive enhancers" defined by verbatim terms: donepezil (Aricept, Adlarity), galantamine (Razadyne, Reminyl), rivastigmine (Exelon) and memantine (Namenda, Ebixa, Nemdatine) will be summarized separately. All concomitant medication data will be listed. The cognitive enhancers

will be flagged in the concomitant medication listing.

9.7. MRI

Descriptive summaries of MRI findings will be presented by treatment group with number and percentage of participants for presence of CS MRI abnormalities, total number of MH, total number of new MH, and total number of resolved MH at the following visits. The Persistence and new occurrence of MRI abnormality will be presented by treatment group at week 40 and week 76.

Baseline, Week 40 and Week 76/ET/ED.

The descriptive analysis will be presented for those subjects who signed consent for MRI sub-study.

The MRI findings will be listed.

9.8. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is routinely used to quantify the presence and severity of suicidal ideation and behavior. Both the ideation and behavior subscales are sensitive to change over time.

Two versions of the C-SSRS will be used in this study: the Baseline/Screening version and the Since Last Visit version. The Baseline/Screening version of the C-SSRS assesses lifetime suicidal ideation and behavior. The Since Last Visit version of the C-SSRS assesses suicidal thoughts or behaviors the participant may have had since the last time the C-SSRS was administered.

At the screening visit, the C-SSRS Baseline/Screening version will be administered. At all subsequent visits (Baseline, Week 4, Week 16, Week 28, Week 40, Week 52, Week 64 and Week 76/ET/ED), the C-SSRS Since Last Visit version will be administered.

The C-SSRS includes “yes” or “no” responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe). A score of 0 is assigned if no ideation is present.

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 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.

Baseline is defined as the most severe ideation and behavior reported prior to the first dose of study drug (C-SSRS assessment date <= first dose date of study drug). Suicidality data collected on the C-SSRS will be listed for all participants. Tables will include results from the Suicidal Ideation and Suicidal Behavior sections of the C-SSRS. The number and percentage of participants with a response of “Yes” at any point as well as by study visit on the Suicidal Ideation and Suicidal Behavior items will be summarized by treatment received.

Additionally, shifts of whether participants experienced suicidal ideation, behavior, or both from

pre-treatment to post-treatment will be summarized in a shift table. An additional shift table of maximum ideation from pre-treatment to post-treatment will also be provided.

All C-SSRS data will be listed.

All other safety evaluations including urine drug screen results, screening laboratory assessments, Genotyping results collected at Baseline (Study Day 1), and Follow-up Phone Call data will be listed.

10. Changes from Planned Analysis

Not Applicable.

11. Other Planned Analysis

11.1. Renal Insufficiency Analysis

The purpose of this analysis is to characterize the effect of renal impairment on the safety, and tolerability of simufilam.

Participants will be categorized into normal renal function or renal impairment groups based on their estimated glomerular filtration rate (eGFR) as shown in the table below.

Table 4: Renal Function Categories by eGFR Ranges

Renal Impairment[a]	Estimated eGFR (mL/min)
None (Normal)	≥ 90
Mild Renal Impairment	60 - 89
Moderate renal impairment	≥30 to <60
Severe Renal Impairment	≥15 to <30

a. Stages of renal impairment are based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2021) – for Adult Participants (≥ 18 years)

11.1.1 Calculation of eGFR:

The eGFR (in mL/min) will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2021) – for Adult Participants (≥ 18 years):

$$eGFR = 142 \times [\min(S_{Cr}/k\,, 1)]^{\alpha} \times [\max(S_{Cr}/k\,, 1)]^{-1.200} \times 0.9938^{Age} \times 1.012\ (if\ female)$$

where

S_{Cr} = standardized serum creatinine in mg/dL

k = 0.7 for females or 0.9 for males

α = -0.241 for females or -0.302 for males

min (S_{Cr}/k, *1*) is the minimum value of S_{Cr}/k or 1.0

max (S_{Cr}/k, *1*) is the maximum value of S_{Cr}/k or 1.0

age in years

As the Creatinine is collected at the visits; Day 1 (Baseline), Week 4, Week 16, Week 40, Week

52, Week 64 and Week 76. eGFR will be calculated at the same visits.

11.1.2 Statistical Methods and Analysis

11.1.2.1 Statistical Summaries on Creatinine, eGFR and Renal Function

The descriptive statistics of the observed and the change from baseline in Creatinine will be summarized by treatment group and renal function through Week 76. The same information will be graphically displayed using a clustered bar chart.

The descriptive summary statistics of eGFR will be presented by treatment group and renal function through Week 76.

The number of participants and percentages of renal function will be presented for the subgroups; MMSE (16-20, 21-27), age (>=75, 65-74, and < 65), sex, and ethnicity, by treatment group at Baseline (Day 1).

11.1.2.2 Statistical Summaries on Select TEAEs vs Renal Function at Baseline (Day 1)

The effect of renal impairment on TEAEs will be characterized by displaying the summary statistics as well as the plots.

A summary of TEAEs by relatedness and renal function derived at Baseline (Day 1) will be provided by treatment groups.

A summary of select TEAEs Incidence by Renal Function derived at Baseline (Day 1) will be provided along with a clustered bar plot, where the select TEAEs of interest (Preferred Terms of the 10 most frequent TEAEs at the end of the study) when assessing the impact of study drug according to renal function.

11.2. Pharmacokinetic Analysis

The PK analysis is being completed by another organization and is not included in this SAP.

12. References

1. Protocol number PTI-125-06, A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 76-Week Study Evaluating the Safety and Efficacy of Two Doses of Simufilam in Subjects with Mild-to-Moderate Alzheimer's Disease, dated 06-FEB-2023 (version 3.0).
2. ASA. (2018) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2018. http://www.amstat.org/about/ethicalguidelines.cfm
3. ICH (1998). ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials E9; 1998. https://database.ich.org/sites/default/files/E9_Guideline.pdf
4. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. https://rss.org.uk/about/policy-and-guidelines/code-of-conduct/.

13. Tables, Listings, and Figures

13.1. Demographic Data Summary Tables and Figures

Table 5: Demographic Data Summary Tables and Figures

Table Number	Population	Table Title/Summary
14.1.1	All Subjects	Subject Disposition (Includes All Early Terminations)
14.1.2.1.1	ITT	Demographics and Baseline Characteristics
14.1.2.1.2	ITT-mild	Demographics and Baseline Characteristics
14.1.2.1.3	mITT	Demographics and Baseline Characteristics
14.1.2.2	Safety	Demographics and Baseline Characteristics
14.1.2.3.1	ITT	Medical History
14.1.2.3.2	ITT-mild	Medical History
14.1.2.4.1.1	ITT	Prior Medications
14.1.2.4.1.2	ITT-mild	Prior Medications
14.1.3.1	Safety	Study Drug Exposure
14.1.3.2	Safety	Study Drug Compliance by Visit
14.1.4.1	ITT	Important Protocol Deviations
14.1.4.2	ITT-mild	Important Protocol Deviations

13.2. Efficacy Data

Table 6: Efficacy Data

Table Number	Population	Table Title/Summary
T14.2.1	mITT	Summary of Primary, Secondary, and Exploratory Endpoints- Primary Efficacy Model
T14.2.1.1.1	mITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment
T14.2.1.2.1	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment
T14.2.1.3.1	cITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment
T14.2.1.4.1	ITT-mild	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment
T14.2.1.1.2	mITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment: Imputation Missing Not at Random
T14.2.1.1.3	mITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment; Post Baseline Dose Change or Concomittant Medication Censoring Sensitivity Analysis
T14.2.1.1.4	mITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment; Intercurrent Event Sensitivity analysis

T14.2.1.5.1	mITT amnestic subset	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment
T14.2.1.2.6	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Mild (21-27)/Moderate(<21) AD Status
T14.2.1.2.7	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by MMSE Total Score ≥20 and ≤27
T14.2.1.2.8	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Age Group
T14.2.1.2.9	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Sex
T14.2.1.2.10	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Race
T14.2.1.2.11	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Ethnicity
T14.2.1.2.12	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by ApoE4 Genotype
T14.2.1.2.13	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Medication Usage
T14.2.1.2.14	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Baseline Severity Group
T14.2.1.2.15	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau 181 Level
T14.2.1.2.16	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment: Responder Analysis
T14.2.1.2.17	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Mild (21-27)/Moderate(<21) AD Status: Responder Analysis
T14.2.1.2.18	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment: Mild to Moderate Progression Analysis
T14.2.1.2.19	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment: Moderate to Severe Progression Analysis
T14.2.1.2.20	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment: Time Component Test
T14.2.1.6.1	Pooled	Summary of Change from Baseline to Week 52 in ADAS-Cog 12 Total Score by Visit and Treatment
T14.2.1.6.2	Pooled	Summary of Change from Baseline to Week 52 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Baseline Severity Group
T14.2.1.6.3	Pooled	Summary of Change from Baseline to Week 52 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau Level
T14.2.2.1.1	mITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment
T14.2.2.2.1	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment
T14.2.2.3.1	cITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment
T14.2.2.4.1	ITT-mild	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment

T14.2.2.1.2	mITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment: Imputation Missing Not at Random
T14.2.2.1.3	mITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment; Post Baseline Dose Change or Concomittant Medication Censoring Sensitivity Analysis
T14.2.2.1.4	mITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment; Intercurrent Event Sensitivity analysis
T14.2.2.5.1	mITT amnestic subset	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment
T14.2.2.2.6	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Mild (21-27)/Moderate(<21) AD Status
T14.2.2.2.7	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by MMSE Total Score ≥20 and ≤27
T14.2.2.2.8	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Age Group
T14.2.2.2.9	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Sex
T14.2.2.2.10	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Race
T14.2.2.2.11	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Ethnicity
T14.2.2.2.12	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by ApoE4 Genotype
T14.2.2.2.13	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Medication Usage
T14.2.2.2.14	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Baseline Severity Group
T14.2.2.2.15	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau 181 Level
T14.2.2.2.16	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment: Responder Analysis
T14.2.2.2.17	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Mild (21-27)/Moderate(<21) AD Status: Responder Analysis
T14.2.2.2.18	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment: Mild to Moderate Progression Analysis
T14.2.2.2.19	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment: Moderate to Severe Progression Analysis
T14.2.2.2.20	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment: Time Component Test
T14.2.2.6.1	Pooled	Summary of Change from Baseline to Week 52 in ADCS-ADL Total Score by Visit and Treatment
T14.2.2.6.2	Pooled	Summary of Change from Baseline to Week 52 in ADCS-ADL Total Score by Visit and Treatment Stratified by Baseline Severity Group
T14.2.2.6.3	Pooled	Summary of Change from Baseline to Week 52 in ADCS-ADL Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau Level
T14.2.3.1.1	mITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment

T14.2.3.2.1	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment
T14.2.3.3.1	cITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment
T14.2.3.4.1	ITT-mild	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment
T14.2.3.5.1	mITT amnestic subset	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment
T14.2.3.2.6	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by Mild (21-27)/Moderate(<21) AD Status
T14.2.3.2.7	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by MMSE Total Score ≥20 and ≤27
T14.2.3.2.8	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by Age Group
T14.2.3.2.9	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by Sex
T14.2.3.2.10	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by Race
T14.2.3.2.11	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by Ethnicity
T14.2.3.2.12	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by ApoE4 Genotype
T14.2.3.2.13	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by Medication Usage
T14.2.3.2.14	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by Baseline Severity Group
T14.2.3.2.15	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau 181 Level
T14.2.3.6.1	Pooled	Summary of Change from Baseline to Week 52 in iADRS Total Score by Visit and Treatment
T14.2.3.6.2	Pooled	Summary of Change from Baseline to Week 52 in iADRS Total Score by Visit and Treatment Stratified by Baseline Severity Group
T14.2.3.6.3	Pooled	Summary of Change from Baseline to Week 52 in iADRS Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau Level
T14.2.4.1.1	mITT	Summary of Change from Baseline to Week 76 in MMSE Total Score by Visit and Treatment
T14.2.4.2.1	ITT	Summary of Change from Baseline to Week 76 in MMSE Total Score by Visit and Treatment
T14.2.4.3.1	cITT	Summary of Change from Baseline to Week 76 in MMSE Total Score by Visit and Treatment
T14.2.4.4.1	ITT-mild	Summary of Change from Baseline to Week 76 in MMSE Total Score by Visit and Treatment
T14.2.4.6.1	Pooled	Summary of Change from Baseline to Week 52 in MMSE Total Score by Visit and Treatment
T14.2.4.6.2	Pooled	Summary of Change from Baseline to Week 52 in MMSE Total Score by Visit and Treatment Stratified by Baseline Severity Group
T14.2.4.6.3	Pooled	Summary of Change from Baseline to Week 52 in MMSE Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau Level
T14.2.5.1.1	mITT	Summary of Change from Baseline to Week 76 in NPI-10 Total Score by Visit and Treatment

T14.2.5.2.1	ITT	Summary of Change from Baseline to Week 76 in NPI-10 Total Score by Visit and Treatment
T14.2.5.3.1	cITT	Summary of Change from Baseline to Week 76 in NPI-10 Total Score by Visit and Treatment
T14.2.5.4.1	ITT-mild	Summary of Change from Baseline to Week 76 in NPI-10 Total Score by Visit and Treatment
T14.2.5.5.1	ITT	Summary of Change from Baseline to Week 76 in NPI-10 Total Score by Visit and Treatment in Participants with a baseline NPI-10 Score ≥2
T14.2.5.6.1	ITT	Summary of Change from Baseline to Week 76 in NPI-10 Agitation and Aggression Domain Scores by Visit and Treatment in Participants with a Non-Zero Baseline Score for that Domain
T14.2.5.7.1	ITT	Summary of Change from Baseline to Week 76 in NPI-10 Total Score by Visit and Treatment: Responder Analysis
T14.2.5.6.1	Pooled	Summary of Change from Baseline to Week 52 in NPI-10 Total Score by Visit and Treatment
T14.2.5.6.2	Pooled	Summary of Change from Baseline to Week 52 in NPI-10 Total Score by Visit and Treatment Stratified by Baseline Severity Group
T14.2.5.6.3	Pooled	Summary of Change from Baseline to Week 52 in NPI-10 Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau Level
T14.2.6.1.1	mITT	Summary of Change from Baseline to Week 76 in ZBI Total Score by Visit and Treatment
T14.2.6.2.1	ITT	Summary of Change from Baseline to Week 76 in ZBI Total Score by Visit and Treatment
T14.2.6.3.1	cITT	Summary of Change from Baseline to Week 76 in ZBI Total Score by Visit and Treatment
T14.2.6.4.1	ITT-mild	Summary of Change from Baseline to Week 76 in ZBI Total Score by Visit and Treatment
T14.2.6.6.1	Pooled	Summary of Change from Baseline to Week 52 in ZBI Total Score by Visit and Treatment
T14.2.6.6.2	Pooled	Summary of Change from Baseline to Week 52 in ZBI Total Score by Visit and Treatment Stratified by Baseline Severity Group
T14.2.6.6.3	Pooled	Summary of Change from Baseline to Week 52 in ZBI Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau Level
T14.2.7.1.1	mITT	Summary of Change from Baseline to Week 76 in CDR-SB Total Score by Visit and Treatment
T14.2.7.2.1	ITT	Summary of Change from Baseline to Week 76 in CDR-SB Total Score by Visit and Treatment
T14.2.7.3.1	cITT	Summary of Change from Baseline to Week 76 in CDR-SB Total Score by Visit and Treatment
T14.2.7.4.1	ITT-mild	Summary of Change from Baseline to Week 76 in CDR-SB Total Score by Visit and Treatment
T14.2.7.6.1	Pooled	Summary of Change from Baseline to Week 52 in CDR-SB Total Score by Visit and Treatment
T14.2.7.6.2	Pooled	Summary of Change from Baseline to Week 52 in CDR-SB Total Score by Visit and Treatment Stratified by Baseline Severity Group
T14.2.7.6.3	Pooled	Summary of Change from Baseline to Week 52 in CDR-SB Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau Level
T14.2.8.1.1	ITT-plasma	Summary of Change from Baseline to week 76 in Plasma P-Tau 217 by Visit and Treatment
T14.2.8.1.2	ITT-CSF	Summary of Change from Baseline to week 76 in CSF P-Tau 217 by Visit and Treatment

T14.2.9.1.1	ITT-plasma	Summary of Change from Baseline to week 76 in Plasma Total Tau by Visit and Treatment
T14.2.9.1.2	ITT-CSF	Summary of Change from Baseline to week 76 in CSF Total Tau by Visit and Treatment
T14.2.10.1.1	ITT-plasma	Summary of Change from Baseline to week 76 in Plasma GFAP by Visit and Treatment
T14.2.10.1.2	ITT-CSF	Summary of Change from Baseline to week 76 in CSF GFAP by Visit and Treatment
T14.2.11.1.1	ITT-plasma	Summary of Change from Baseline to week 76 in Plasma NfL by Visit and Treatment
T14.2.11.1.2	ITT-CSF	Summary of Change from Baseline to week 76 in CSF NfL by Visit and Treatment
T14.2.12.1.1	PET	Summary of Change from Baseline to week 76 in tau PET by Visit and Treatment
T14.2.12.1.2	PET	Summary of Change from Baseline to week 76 in amyloid PET by Visit and Treatment
T14.2.13.1.1	MRI	Summary of Change from Baseline to week 76 in Whole Brain Volume by Visit and Treatment
T14.2.13.1.2	MRI	Summary of Change from Baseline to week 76 in Ventricular Volume by Visit and Treatment
T14.2.14.1.1	MRI	Summary of Change from Baseline to week 76 in Hippocampal Volume by Visit and Treatment
T14.2.14.1.2	MRI	Summary of Change from Baseline to week 76 in Cortical Thickness Volume by Visit and Treatment

13.3. Safety Data

Table 7: Safety Data

Table Number	Population	Table Title/Summary
14.3.1 Displays of Adverse Events		
14.3.1.1	Safety	Overall Summary of Treatment Emergent Adverse Events
14.3.1.2	Safety	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term
14.3.1.3	Safety	Summary of Treatment Emergent Drug-Related Adverse Events by System Organ Class and Preferred Term
14.3.1.4	Safety	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity
14.3.1.5	Safety	Summary of Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term
14.3.1.6	Safety	Summary of Treatment Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term
14.3.2 Summary of Deaths, Other Serious and Significant Adverse Events		
14.3.2.1	Safety	Listing of Serious Adverse Events
14.3.2.2	Safety	Listing of Adverse Events Leading to Study Discontinuation
14.3.2.3	Safety	Listing of Adverse Events Leading to Death
14.3.5 Laboratory Data Summary Tables		

Table Number	Population	Table Title/Summary
14.3.5.1.1	Safety	Summary of Laboratory Results - Serum Chemistry
14.3.5.1.2	Safety	Summary of Shift from Baseline in Serum Chemistry Results
14.3.5.2.1	Safety	Summary of Laboratory Results-Hematology
14.3.5.2.2	Safety	Summary of Shift from Baseline in Hematology Results
14.3.5.3.1	Safety	Summary of Laboratory Results -Urinalysis
14.3.5.3.2	Safety	Summary of Categorical Urinalysis Results
14.3.5.4	Safety	Summary of Stopping Criteria by Treatment
14.3.6 Other Safety Data Summary Tables		
14.3.6.1	Safety	Summary of Vital Signs Results
14.3.6.2	Safety	Summary of Weights and BMI
14.3.7.1	Safety	Summary of Concomitant Medications
14.3.7.2	Safety	Summary of Concomitant Medications-Cognitive Enhancers Taken Prior to First Dose of Study Drug
14.3.7.3	Safety	Summary of Concomitant Medications-Cognitive Enhancers Taken Post First Dose of Study Drug
14.3.8.1	Safety	Summary of Electrocardiogram Quantitative Results
14.3.8.2	Safety	Summary of Electrocardiogram Interpretation Results
14.3.8.3	Safety	Summary of Observed Categorical ECGs
14.3.8.4	Safety	Summary of Change from Baseline Categorical ECGs
14.3.9.1	Safety	Summary of Physical Examination (Brief) Results
14.3.9.2	Safety	Summary of Neurological Examination (Brief) Results
14.3.10.1	Safety	Summary of Columbia-Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation and Suicidal Behavior Experienced at Any Time Post-Treatment
14.3.10.2	Safety	Summary of Columbia-Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation and Suicidal Behavior by Study Visit
14.3.10.3	Safety	Shift of Columbia-Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation and Suicidal Behavior from Pre-Treatment to Post-Treatment
14.3.10.4	Safety	Shift of Columbia-Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation Scores from Baseline to Treatment Period
14.3.11.1	MRI Sub-study	Summary of MRI Findings
14.3.5 Other Data Summary Tables		
14.5.1.1	Safety	Summary of Creatinine (umol/L) by Renal Function by Visit
14.5.1.2	Safety	Summary of eGFR (mL/min) by Renal Function by Visit
14.5.1.3	Safety	Summary of Renal Function by Subgroups at Baseline
14.5.2.1	Safety	Summary of TEAEs by Relatedness by Renal Function
14.5.2.2	Safety	Summary of Select TEAEs by Renal Function

13.4. Planned Listing Descriptions

The following are planned data and participant data listings for protocol number PTI-125-06.

In general, one listing will be produced per CRF domain. All listings will be sorted by treatment, and participant number. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each participant. Within a data listing, if an item appears line after line (e.g., repetition of participant number), then only the first occurrence will be displayed.

In data listings, the information for one participant will be kept on one page if at all possible, rather than splitting a participant's information across pages.

Table 8: Planned Listings

Data Listing Number	Table Title/Summary
16.2 Subject Data Listings	
16.2.1 Subject Discontinuations/Completions	
16.2.1.1	Subject Disposition
16.2.1.2	Inclusion and Exclusion Criteria
16.2.1.3	Subject Randomization
16.2.2 Protocol Deviations	
16.2.2	Protocol Deviations
16.2.3 Subjects Excluded from the Efficacy Analyses	
16.2.3	Analysis Populations
16.2.4 Demographic Data and Other Baseline Characteristics	
16.2.4.1	Demographic and Baseline Characteristics
16.2.4.2	Medical or Surgical History
16.2.4.3	Alzheimer's Disease History
16.2.4.4	COVID-19 History
16.2.4.5	Brain MRI
16.2.5 Compliance and/or Drug Concentration Data	
16.2.5.1	Study Drug Administration
16.2.5.2	Drug Accountability
16.2.5.3	Compliance
16.2.6 Individual Efficacy Response Data	
L16.2.xx.xx	Listing of ADAS-Cog Total Score by Treatment, Visit, and MMSE Mild/Moderate Status
L16.2.xx.xx	Listing of ADCS-ADL Total Score by Treatment, Visit, and MMSE Mild/Moderate Status
L16.2.xx.xx	Listing of iADRS Total Score by Treatmen, Visit, and MMSE Mild/Moderate Status

Data Listing Number	Table Title/Summary
L16.2.xx.xx	Listing of MMSE Total Score by Treatment, Visit, and MMSE Mild/Moderate Status
L16.2.xx.xx	Listing of NPI-10 Total Score by Treatment, Visit, and MMSE Mild/Moderate Status
L16.2.xx.xx	Listing of NPI-10 Agitation and Aggression Domain Scores by Treatment, Visit, and MMSE Mild/Moderate Status
L16.2.xx.xx	Listing of ZBI Total Score by Treatment, Visit, and MMSE Mild/Moderate Status
L16.2.xx.xx	Listing of CDR-SB Score by Treatment, Visit, and MMSE Mild/Moderate Status
L16.2.xx.xx	Listing of Plasma Biomarkers by Visit and Treatment
L16.2.xx.xx	Listing of CSF Biomarkers by Visit and Treatment
L16.2.xx.xx	Listing of Volumetric MRI Biomarkers by Visit and Treatment
16.2.7 Adverse Event Listings	
16.2.7.1	Treatment Emergent Adverse Events
16.2.7.2.	Select Treatment Emergent Adverse Events Used for Renal Function
16.2.8 Laboratory Values (by Subject)	
16.2.8.1.1	Laboratory Results: Serum Chemistry
16.2.8.1.2	Laboratory Results: Hematology
16.2.8.1.3	Laboratory Results: Urinalysis
16.2.8.1.4	Screening Laboratory Assessments
16.2.8.2	Urine Drug Screen
16.2.8.3	Genotyping Sample Collection
16.2.8.4	Pharmacokinetic Results
16.2.8.5	Subjects Who Met Stopping Criteria
16.2.8.6	Creatinine, eGFR, and Renal Function
16.2.9 Other Clinical Observations and Measurements (by Subject)	
16.2.9.1.1.1	Physical Examination (Complete)
16.2.9.1.1.2	Physical Examination (Brief)
16.2.9.1.2.1	Neurologic Examination (Complete)
16.2.9.1.2.2	Neurologic Examination (Brief)
16.2.9.2.1	Vital Signs
16.2.9.3.1	Prior and Concomitant Medications
16.2.9.3.2	Concomitant Medications – Cognitive Enhancers
16.2.9.4.1	12-Lead Electrocardiogram (ECG) Quantitative Results
16.2.9.4.2	12-Lead Electrocardiogram (ECG) Categorical Results
16.2.9.5	Columbia-Suicide Severity Rating Scale (C-SSRS)
16.2.9.6.1	COVID-19 Impact

Data Listing Number	Table Title/Summary
16.2.9.6.2	COVID-19 Study Drug Impact
16.2.9.7	Follow-up Phone Calls

13.5. Planned Figure Descriptions

The following are planned summary figures for protocol number PTI-125-06. The figure numbers and page numbers are place holders only and will be determined when the figures are produced.

Table 9: Planned Figures

Figure Number	Population	Figure Title/Summary
14.6.1.1	Safety	Plot of Creatine (umol/L) Changes from Baseline by Renal Function and Treatment at Each Post-Baseline Visit
14.6.1.2	Safety	Plot of eGFR (mL/min) Changes from Baseline by Renal Function and Treatment at Each Post-Baseline Visit
14.6.2.1	Safety	Plot of Drug-Related TEAEs by Renal Function and Treatment
14.6.2.2	Safety	Plot of Select TEAEs by Renal Function and Treatment
Efficacy		
F14.2.1	mITT	Summary of Primary, Secondary, and Exploratory Endpoints-Primary Efficacy Model
F14.2.1.1.1	mITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment
F14.2.1.2.1	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment
F14.2.1.3.1	cITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment
F14.2.1.4.1	ITT-mild	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment
F14.2.1.1.2	mITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment: Imputation Missing Not at Random
F14.2.1.1.3	mITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment; Post Baseline Dose Change or Concomittant Medication Censoring Sensitivity Analysis
F14.2.1.1.4	mITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment; Intercurrent Event Sensitivity analysis
F14.2.1.5.1	mITT amnestic subset	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment
F14.2.1.2.6	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Mild (21-27)/Moderate(<21) AD Status

Figure Number	Population	Figure Title/Summary
F14.2.1.2.7	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by MMSE Total Score ≥20 and ≤27
F14.2.1.2.8	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Age Group
F14.2.1.2.9	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Sex
F14.2.1.2.10	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Race
F14.2.1.2.11	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Ethnicity
F14.2.1.2.12	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by ApoE4 Genotype
F14.2.1.2.13	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Medication Usage
F14.2.1.2.14	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Baseline Severity Group
F14.2.1.2.15	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau 181 Level
F14.2.1.2.16	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment: Responder Analysis
F14.2.1.2.17	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment Mild (21-27)/Moderate(<21) AD Status: Responder Analysis
F14.2.1.2.18	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment: Mild to Moderate Progression Analysis
F14.2.1.2.19	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment: Moderate to Severe Progression Analysis
F14.2.1.2.20	ITT	Summary of Change from Baseline to Week 76 in ADAS-Cog 12 Total Score by Visit and Treatment: Time Component Test
F14.2.1.6.1	Pooled	Summary of Change from Baseline to Week 52 in ADAS-Cog 12 Total Score by Visit and Treatment
F14.2.1.6.2	Pooled	Summary of Change from Baseline to Week 52 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Baseline Severity Group
F14.2.1.6.3	Pooled	Summary of Change from Baseline to Week 52 in ADAS-Cog 12 Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau Level
F14.2.2.1.1	mITT	Summary of Change from Baseline to Week 76 in ADCS-ADL

Figure Number	Population	Figure Title/Summary
		Total Score by Visit and Treatment
F14.2.2.2.1	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment
F14.2.2.3.1	cITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment
F14.2.2.4.1	ITT-mild	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment
F14.2.2.1.2	mITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment: Imputation Missing Not at Random
F14.2.2.1.3	mITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment; Post Baseline Dose Change or Concomittant Medication Censoring Sensitivity Analysis
F14.2.2.1.4	mITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment; Intercurrent Event Sensitivity analysis
F14.2.2.5.1	mITT amnestic subset	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment
F14.2.2.2.6	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Mild (21-27)/Moderate(<21) AD Status
F14.2.2.2.7	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by MMSE Total Score ≥20 and ≤27
F14.2.2.2.8	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Age Group
F14.2.2.2.9	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Sex
F14.2.2.2.10	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Race
F14.2.2.2.11	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Ethnicity
F14.2.2.2.12	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by ApoE4 Genotype
F14.2.2.2.13	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Medication Usage
F14.2.2.2.14	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Baseline Severity Group
F14.2.2.2.15	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau 181 Level
F14.2.2.2.16	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL

Figure Number	Population	Figure Title/Summary
		Total Score by Visit and Treatment: Responder Analysis
F14.2.2.2.17	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment Mild (21-27)/Moderate(<21) AD Status: Responder Analysis
F14.2.2.2.18	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment: Mild to Moderate Progression Analysis
F14.2.2.2.19	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment: Moderate to Severe Progression Analysis
F14.2.2.2.20	ITT	Summary of Change from Baseline to Week 76 in ADCS-ADL Total Score by Visit and Treatment: Time Component Test
F14.2.2.6.1	Pooled	Summary of Change from Baseline to Week 52 in ADCS-ADL Total Score by Visit and Treatment
F14.2.2.6.2	Pooled	Summary of Change from Baseline to Week 52 in ADCS-ADL Total Score by Visit and Treatment Stratified by Baseline Severity Group
F14.2.2.6.3	Pooled	Summary of Change from Baseline to Week 52 in ADCS-ADL Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau Level
F14.2.3.1.1	mITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment
F14.2.3.2.1	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment
F14.2.3.3.1	cITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment
F14.2.3.4.1	ITT-mild	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment
F14.2.3.5.1	mITT amnestic subset	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment
F14.2.3.2.6	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by Mild (21-27)/Moderate(<21) AD Status
F14.2.3.2.7	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by MMSE Total Score ≥20 and ≤27
F14.2.3.2.8	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by Age Group
F14.2.3.2.9	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by Sex
F14.2.3.2.10	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by Race
F14.2.3.2.11	ITT	Summary of Change from Baseline to Week 76 in iADRS Total

Figure Number	Population	Figure Title/Summary
		Score by Visit and Treatment Stratified by Ethnicity
F14.2.3.2.12	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by ApoE4 Genotype
F14.2.3.2.13	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by Medication Usage
F14.2.3.2.14	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by Baseline Severity Group
F14.2.3.2.15	ITT	Summary of Change from Baseline to Week 76 in iADRS Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau 181 Level
F14.2.3.6.1	Pooled	Summary of Change from Baseline to Week 52 in iADRS Total Score by Visit and Treatment
F14.2.3.6.2	Pooled	Summary of Change from Baseline to Week 52 in iADRS Total Score by Visit and Treatment Stratified by Baseline Severity Group
F14.2.3.6.3	Pooled	Summary of Change from Baseline to Week 52 in iADRS Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau Level
F14.2.4.1.1	mITT	Summary of Change from Baseline to Week 76 in MMSE Total Score by Visit and Treatment
F14.2.4.2.1	ITT	Summary of Change from Baseline to Week 76 in MMSE Total Score by Visit and Treatment
F14.2.4.3.1	cITT	Summary of Change from Baseline to Week 76 in MMSE Total Score by Visit and Treatment
F14.2.4.4.1	ITT-mild	Summary of Change from Baseline to Week 76 in MMSE Total Score by Visit and Treatment
F14.2.4.6.1	Pooled	Summary of Change from Baseline to Week 52 in MMSE Total Score by Visit and Treatment
F14.2.4.6.2	Pooled	Summary of Change from Baseline to Week 52 in MMSE Total Score by Visit and Treatment Stratified by Baseline Severity Group
F14.2.4.6.3	Pooled	Summary of Change from Baseline to Week 52 in MMSE Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau Level
F14.2.5.1.1	mITT	Summary of Change from Baseline to Week 76 in NPI-10 Total Score by Visit and Treatment
F14.2.5.2.1	ITT	Summary of Change from Baseline to Week 76 in NPI-10 Total Score by Visit and Treatment
F14.2.5.3.1	cITT	Summary of Change from Baseline to Week 76 in NPI-10 Total Score by Visit and Treatment
F14.2.5.4.1	ITT-mild	Summary of Change from Baseline to Week 76 in NPI-10 Total Score by Visit and Treatment
F14.2.5.5.1	ITT	Summary of Change from Baseline to Week 76 in NPI-10 Total Score by Visit and Treatment in Participants with a baseline NPI-10

Figure Number	Population	Figure Title/Summary
		Score ≥2
F14.2.5.6.1	ITT	Summary of Change from Baseline to Week 76 in NPI-10 Agitation and Aggression Domain Scores by Visit and Treatment in Participants with a Non-Zero Baseline Score for that Domain
F14.2.5.7.1	ITT	Summary of Change from Baseline to Week 76 in NPI-10 Total Score by Visit and Treatment: Responder Analysis
F14.2.5.6.1	Pooled	Summary of Change from Baseline to Week 52 in NPI-10 Total Score by Visit and Treatment
F14.2.5.6.2	Pooled	Summary of Change from Baseline to Week 52 in NPI-10 Total Score by Visit and Treatment Stratified by Baseline Severity Group
F14.2.5.6.3	Pooled	Summary of Change from Baseline to Week 52 in NPI-10 Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau Level
F14.2.6.1.1	mITT	Summary of Change from Baseline to Week 76 in ZBI Total Score by Visit and Treatment
F14.2.6.2.1	ITT	Summary of Change from Baseline to Week 76 in ZBI Total Score by Visit and Treatment
F14.2.6.3.1	cITT	Summary of Change from Baseline to Week 76 in ZBI Total Score by Visit and Treatment
F14.2.6.4.1	ITT-mild	Summary of Change from Baseline to Week 76 in ZBI Total Score by Visit and Treatment
F14.2.6.6.1	Pooled	Summary of Change from Baseline to Week 52 in ZBI Total Score by Visit and Treatment
F14.2.6.6.2	Pooled	Summary of Change from Baseline to Week 52 in ZBI Total Score by Visit and Treatment Stratified by Baseline Severity Group
F14.2.6.6.3	Pooled	Summary of Change from Baseline to Week 52 in ZBI Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau Level
F14.2.7.1.1	mITT	Summary of Change from Baseline to Week 76 in CDR-SB Total Score by Visit and Treatment
F14.2.7.2.1	ITT	Summary of Change from Baseline to Week 76 in CDR-SB Total Score by Visit and Treatment
F14.2.7.3.1	cITT	Summary of Change from Baseline to Week 76 in CDR-SB Total Score by Visit and Treatment
F14.2.7.4.1	ITT-mild	Summary of Change from Baseline to Week 76 in CDR-SB Total Score by Visit and Treatment
F14.2.7.6.1	Pooled	Summary of Change from Baseline to Week 52 in CDR-SB Total Score by Visit and Treatment
F14.2.7.6.2	Pooled	Summary of Change from Baseline to Week 52 in CDR-SB Total Score by Visit and Treatment Stratified by Baseline Severity Group
F14.2.7.6.3	Pooled	Summary of Change from Baseline to Week 52 in CDR-SB Total Score by Visit and Treatment Stratified by Baseline Plasma P-Tau Level

Figure Number	Population	Figure Title/Summary
F14.2.8.1.1	ITT-plasma	Summary of Change from Baseline to week 76 in Plasma P-Tau 217 by Visit and Treatment
F14.2.8.1.2	ITT-CSF	Summary of Change from Baseline to week 76 in CSF P-Tau 217 by Visit and Treatment
F14.2.9.1.1	ITT-plasma	Summary of Change from Baseline to week 76 in Plasma Total Tau by Visit and Treatment
F14.2.9.1.2	ITT-CSF	Summary of Change from Baseline to week 76 in CSF Total Tau by Visit and Treatment
F14.2.10.1.1	ITT-plasma	Summary of Change from Baseline to week 76 in Plasma GFAP by Visit and Treatment
F14.2.10.1.2	ITT-CSF	Summary of Change from Baseline to week 76 in CSF GFAP by Visit and Treatment
F14.2.11.1.1	ITT-plasma	Summary of Change from Baseline to week 76 in Plasma NfL by Visit and Treatment
F14.2.11.1.2	ITT-CSF	Summary of Change from Baseline to week 76 in CSF NfL by Visit and Treatment
F14.2.12.1.1	PET	Summary of Change from Baseline to week 76 in tau PET by Visit and Treatment
F14.2.12.1.2	PET	Summary of Change from Baseline to week 76 in amyloid PET by Visit and Treatment
F14.2.13.1.1	MRI	Summary of Change from Baseline to week 76 in Whole Brain Volume by Visit and Treatment
F14.2.13.1.2	MRI	Summary of Change from Baseline to week 76 in Ventricular Volume by Visit and Treatment
F14.2.14.1.1	MRI	Summary of Change from Baseline to week 76 in Hippocampal Volume by Visit and Treatment
F14.2.14.1.2	MRI	Summary of Change from Baseline to week 76 in Cortical Thickness Volume by Visit and Treatment