Project:

CASSAVA

Protocol:

PTI-125-09

Document:

ABBREVIATED STATISTICAL ANALYSIS PLAN

version:

Live v1.0

Protocol Title:	An Open-Label Extension of the PTI-125-04 Study Evaluating the Safety and Long-Term Treatment of Simufilam in Mild-to-Moderate Alzheimer's Disease Patients
Protocol Number	PTI-125-09
Phase	Phase 2b
Sponsor	**Cassava Sciences, Inc.** 6801 N. Capital of Texas Hwy, Bldg. 1, Ste. 300 Austin, TX 78731
SAP Date:	10-Feb-2025
Status	Live v1.0

Approval Sheet

The undersigned have reviewed and approved this Statistical Analysis Plan for use in this study.

Ben Murray
Electronically signed by: Ben Murray
Reason: I approve this document
Date: Feb 7, 2025 15:19 CST

07-Feb-2025
Date

Ben Murray, MS
Sr. Associate Director,
Clinical Project Management
Cassava Sciences, Inc

Jim Kupiec
Electronically signed by: Jim Kupiec
Reason: I approve this document
Date: Feb 7, 2025 16:21 EST

07-Feb-2025
Date

James W. Kupiec, MD
Chief Medical Officer
Cassava Sciences, Inc

Prashant Kulkarni
Electronically signed by: Prashant Kulkarni
Reason: I approve this document
Date: Feb 10, 2025 14:19 GMT+5.5

10-Feb-2025
Date

Prashant Kulkarni
Lead Biostatistician
Axiom Real-Time Metrics

Note: The issuance date of the Statistical Management Plan is equivalent to the date of final approval.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Only abbreviations and terms relevant to the SAP are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

AD	Alzheimer's Disease
AE	Adverse Event
B.I.D	Twice a day/twice daily
CRF	Clinical Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Min-Mental Status Exam

NTF	Note to File
OLE	Open Label Extension
PT	Preferred Term
SAE	Serious Adverse Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

2. INTRODUCTION

2.1. Preface

This document presents an abbreviated statistical analysis plan (SAP) for Cassava Sciences' open-label extension (OLE) Protocol PTI-125-09 for the Treatment of Alzheimer's Disease. An abbreviated SAP is being prepared as the study and the program are being closed. A full Clinical Study Report (CSR) is not expected to be prepared, but safety data will be provided to allow for inclusion in the Development Safety Update Report (DSUR) later in 2025.

Reference materials for this statistical plan includes Protocol PTI-125-09. The latest version of this protocol is Amendment #3, Dated: September 18, 2024. Amendment #3 allowed for the OLE study to be extended through FDA approval of simufilam or program termination. The program was terminated shortly after approval of this amended protocol by the Central IRB.

The abbreviated statistical analysis plan (SAP) described hereafter is an *a priori* plan. The abbreviated SAP will be finalized and approved prior to database lock.

2.2. Purpose of Analyses

The purpose of this abbreviated Statistical Analysis Plan (SAP) is to provide a description of the statistical methods used to present safety results consistent with protocol PTI-125-09: "An Open-Label Extension of the PTI-125-04 Study Evaluating the Safety and Long-Term Treatment of Simufilam in Mild-to-

Moderate Alzheimer's Disease Patients." Simufilam is an investigational drug candidate under development by the protocol Sponsor, Cassava Sciences, Inc.

Results from these analyses may be used in the DSUR planned for submission in 2025.

Post-hoc exploratory analyses not identified in this SAP are not expected, but may be performed to further examine the study data. These analyses will be clearly identified, where appropriate, in the final clinical study report. Additional analyses not prospectively identified in this SAP may also be completed for publications, or regulatory or funding inquiries. These analyses, if performed, may not be reported in the clinical study report, but will be fully documented in the document containing the additional analyses.

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

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

2.3. Summary of Statistical Analysis Changes to the Protocol

The analyses described in this analysis plan have been modified from the analyses described in the study protocol.

3. STUDY ENDPOINTS

3.1. Primary Endpoint

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

Descriptive summary of vital signs, clinical laboratory parameters, and ECG results during the treatment period will not be performed, as identified in the protocol. Significant results of these assessments, as assessed by the Investigators, will be captured as treatment emergent AEs and SAEs and summarized in basic safety tabulations and provided in data listings.

4. STUDY METHODS

4.1. General Study Design and Plan

This is a 96 week extension study of open-label simufilam 100 mg b.i.d. for subjects who completed the Phase 2 study, PTI-125-04 or who already completed participation in the PTI-125-09 study through Week 96 visit and reconsented to resume participation in the study through FDA approval of simufilam or program termination (Figure 1). All subjects will provide consent to enroll into this study. Simufilam will be administered as coated oral tablets.

The last study visit, Month 24, from the PTI-125-04 study will be used for the Study Day 1 visit assessments in this extension study. Clinic visits will occur every 12 weeks ±10 days as outlined in Table 1– Schedule of Events for Active Participants.

Subjects who already completed participation through Week 96 in PTI-125-09 will have the option to return to the study and resume participation. After the subject provides consent, the Investigator will confirm that the subject continues to satisfy both the inclusion and exclusion criteria. The study drug will be administered at the research site on Re-entry Day 1 and subsequent visits will be scheduled. The length of their participation gap will dictate which visits apply to them according to Table 2 – Schedule of Events for Re-entry Participants.

For active subjects, a full physical examination (general appearance, chest/lungs, heart, abdomen, skin, musculoskeletal, Neurologic, Vascular, and Immunologic) will be performed at Study Day 1, Week 48, and Week 96, and Repeat Visit B until study end. For re-entry subjects, a full physical examination will occur on Re-entry Day 1 and Repeat Visit B thereafter until study ends. All subjects will return to the clinic every 12 weeks for AE monitoring, vital sign measurements, height, weight, Columbia Suicide Severity Rating Scale (C-SSRS) Since Last Visit version, and drug dispensation and accountability. Some re-entry participants will require a Re-entry week 4 visit. A brief physical exam (general appearance, cardiovascular, pulmonary, and abdominal examination, as well as an examination of any other system in response to subject-reported symptoms) will occur at all visits that do not have a full physical exam.

Blood draws for clinical laboratory testing, urine collection for urinalysis, and ECGs will be performed at Study Day 1, Weeks 24, 48, 72, and 96, Re-entry Day 1 (if applicable), Re-Entry Week 4 (if applicable), and Repeat Visit B until study end.

Safety will be evaluated by adverse event monitoring, to include all procedural assessments (e.g., vital signs, clinical labs, ECGs, physical exam, and the C-SSRS), if results of these assessments meet the definition of an AE or SAE, as determined by the Investigator.

Figure 1 - Study Design Schematic

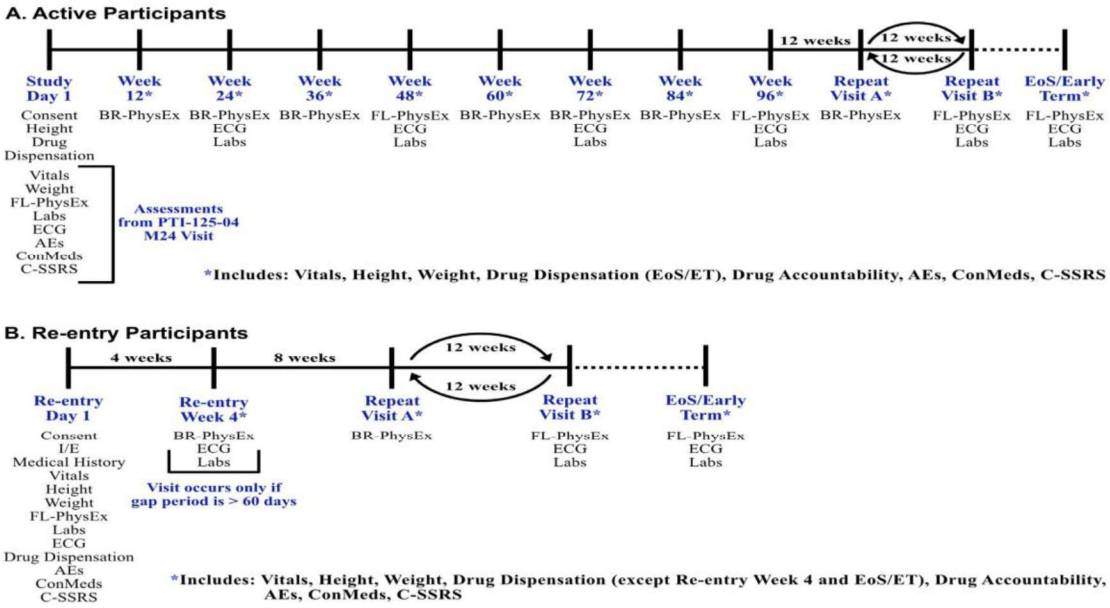

Table 1 - Schedule of Events for Active Participants.

STUDY PROCEDURE	Study Day 1 [a]	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Repeat Visit A [e]	Repeat Visit B [f]	End of Study / Early Term
Informed Consent	X											
Vital Signs	X [b]	X	X	X	X	X	X	X	X	X	X	X
Height & Weight	X [b]	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X [b c]	*	*	*	X [c]	*	*	*	X [c]	*	X c	X [c]
Chemistry, Hematology, Urinalysis	X [b]		X		X		X		X		X	X
ECG	X [b]		X		X		X		X		X	X
Drug Dispensation [d]	X	X	X	X	X	X	X	X	X	X	X	
Drug Accountability		X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X [b]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X [b]	X	X	X	X	X	X	X	X	X	X	X
C-SSRS – Since Last Visit	X [b]	X	X	X	X	X	X	X	X	X	X	X

* Brief physical exam.

[a] Study Day 1 will take place during the Month 24 Visit for study PTI-125-04.

[b] Data collected at Month 24 Visit for study PTI-125-04 will be used.

[c] Full physical examination at Day 1 (as part of Month 24 Visit from study PTI-125-04), Week 48, Week 96, and Repeat Visit B, and at End of Study or Early Term Visit.

[d] Drug will be dispensed at Study Day 1 and every 12 weeks.

[e] Repeat Visit A occurs 12 weeks following the Week 96 visit and then reoccurs every 24 weeks thereafter. [f] Repeat Visit B occurs 12 weeks following the first Repeat Visit A and then reoccurs every 24 weeks thereafter.

Table 2 – Schedule of Events for Re-entry Participants.

STUDY PROCEDURE	Re-entry Day 1	Re-entry Week 4 [e]	Repeat Visit A [c]	Repeat Visit B [d]	End of Study / Early Term
Informed Consent	X				
Medical History	X				
Inclusion/Exclusion Criteria	X				
Vital Signs	X	X	X	X	X
Height & Weight	X	X	X	X	X
Physical Examination	X [a]	*	*	X[a]	X [a]
Chemistry, Hematology, Urinalysis	X	X		X	X
ECG	X	X		X	X
Drug Dispensation [b]	X		X	X	
Drug Accountability		X	X	X	X
Adverse Events	X	X	X	X	X
Concomitant Medications	X	X	X	X	X
C-SSRS – Since Last Visit	X	X	X	X	X

* Brief physical exam.
a Full physical examination at Re-entry Day 1, Repeat Visit B, and at End of Study or Early Term Visit.
b Drug will be dispensed at Re-entry Day 1 and every 12 weeks thereafter.
c Repeat Visit A occurs 12 weeks following the Re-entry Day 1 visit and then reoccurs every 24 weeks thereafter.
d Repeat Visit B occurs 12 weeks following the first Repeat Visit A and then reoccurs every 24 weeks thereafter.
e Re-entry Week 4 visit only for subjects who completed the PTI-125-09 study >60 days prior to completing Re-entry Day 1.

4.2. Inclusion-Exclusion Criteria and General Study Population

All subjects must comply with the following Inclusion Criteria:

1. Must have completed the PTI-125-04 study or Week 96 in the PTI-125-09 study.

2. Male subjects must be willing to continue use of contraception during the study. With female partners of childbearing potential, male subjects, regardless of their fertility status, must agree to either remain abstinent or use condoms in combination with one additional highly effective method of contraception (e.g., oral or implanted contraceptives, or intrauterine devices) or an effective method of contraception (e.g., diaphragms with spermicide or cervical sponges) during the study and for 14 days after study drug dosing has been completed.

Subjects meeting the following Exclusion Criterion will be excluded from the study:

1. Anything that in the opinion of the Investigator would preclude participation in this extension study. For anyone resuming study participation, any significant medical event or hospitalization during the gap period must be discussed with the medical monitor.

5. SAMPLE SIZE

Up to 180 subjects may be enrolled in this study. Eligible subjects include those who completed PTI-125-04.

6. GENERAL ANALYSIS CONSIDERATIONS

6.1. Analysis Population

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

6.2. Covariates and Subgroups

6.2.1. Planned Covariates

No covariates are planned for the analyses.

6.2.2. Planned Subgroups

No subgroups are planned for the analyses.

6.3. Management of Analysis Data

6.3.1. Definition of Analysis Timepoints

Scheduled analysis visits are visits upon scheduled time points as specified in Table 1 - Schedule of Events for Active Participants and Table 2 – Schedule of Events for Re-entry Participants.

There will be no analyses performed based upon analysis timepoints.

6.3.2. Missing Data

Partial or Missing Dates:
Missing data will not be imputed for the purpose of primary inference. All data recorded on the electronic case report form (eCRF) will be included in the safety data listings.

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

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

- If year is present but month and day are missing, impute start date as first dose date if the year is the same as the year of first dose date, otherwise January 1 of that year and impute stop date as last dose date if the year is the same, otherwise December 31 of that year.
- If year and day are present but month is missing, impute start month as first dose date month if AE start day greater than or equal to first dose day and if the year is the same, otherwise January and impute stop month as last dose date month if AE end day less than or equal to last dose day and if the year is the same, otherwise December of that year.
- If year and month are present but day is missing, impute start date as first dose day if the year and month are the same as the year and month of first dose date, otherwise first day of that month and impute stop date as last dose day if year and month are the same, otherwise last day of that month.

6.3.2.1. Imputation Methods

Observed cases, without imputation, will be used for the analyses.

If the relationship of an AE is missing, it will be considered treatment-related. Missing AE severity will be coded as severe.

6.3.3. Handling of Early Termination Visit Information

If a participant is terminated early from this study the early termination visit data will be analyzed at the closest scheduled visit. If the closest visit has valid data, the early termination data will be assigned to the next available visit.

6.3.4. Coding Conventions for Events and Medications

All adverse events will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 27.0) system for reporting (preferred term and body system). Medical history will not be coded.

Prior and concomitant medications will not be coded.

6.3.5. Analysis Software

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

6.3.6. Study Data

Study data identified in the schedule for time and events (Table 1) are collected, and source verified, on the electronic data capture tool: Axiom Fusion eClinical Suite (Axiom, Toronto, ON, Canada).

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

The following Implementation Guides will be referenced for the configuration of SDTM and

ADaM datasets:

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

6.4. Planned Study Analyses

6.4.1. Statistical Summaries: Descriptive and Inferential

The classical summary of count and percentages will be provided for basic safety tabulation and dispositions as appropriate. All data will be presented in by-subject data listings.

No inferential statistics will be produced.

6.4.2. Interim Analyses

No formal interim analyses will be conducted.

7. SUMMARY OF STUDY DATA

7.1. Subject Disposition

A summary of the analysis sets includes the number and percentage for the following categories

- the number of subjects dosed in the original parent study (PTI-125-04 Safety Population)
- the number enrolled in the OLE (OLE Safety Population)
- the number of subjects who completed 96 weeks in the OLE (OLE Safety Population)
    - subject who completed 96 weeks in the OLE and reconsented and resumed study participation (OLE Safety Population) will be identified via footnote
- the number of subjects who discontinued treatment early in the OLE and reason(s) for discontinuation of treatment as recorded on the OLE eCRF

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

7.2. Protocol Deviations

Protocol deviations will not be presented in a data listing, as all subjects who received one dose of study drug during the OLE study will be included in the Subject Disposition and AE tabulations and individual Disposition and AE listings.

7.3. Demographics and Baseline Characteristics

Individual participant demographics and baseline characteristics will be summarized and presented in data listings.

7.4. Medical and Surgical History

Re-entry of subjects based on current medical / surgical history was assessed by Investigator. These will not be presented in data listings, but are available in the source documents at the sites.

7.5. Prior and Concomitant Medications

Medication data will not be presented in data listings.

Study medication compliance will not be calculated. All subjects who took at least one dose of study drug will be included in the Subject Disposition and AE tabulations and individual Disposition and AE listings.

7.6. Concomitant Procedures/Non-drug Therapies

Concomitant Procedures/Non-Drug Therapies data will not be presented in data listings.

8. SAFETY ANALYSES

All safety analyses will be conducted using the Safety population.

8.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary (v27.0) will be used for coding AEs on the OLE Adverse Event eCRF.

Analyses of AEs will be performed for those events that are considered treatment emergent (TEAE), where treatment emergent is defined as any AE with onset or worsening on or after the First Study Dose in the OLE study and will be summarized for overall safety population.

The following summary tables will be presented:

- Overall Summary of TEAEs
- TEAEs by system organ class (SOC) and preferred term (PT)
- TEAEs by PT
- TEAEs by SOC, PT, and Maximum Severity
- TEAEs by SOC, PT, and Relationship to Study Drug
- Treatment Emergent Serious AEs (TESAEs) by SOC and PT

- Treatment Emergent Serious AEs (TESAEs) leading to discontinuation of study by SOC and PT

If more than one event occurred with the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe or related occurrence for the summary by severity, or relationship to study drug, respectively.

The following listing will be created:

- All TEAEs
- All TESAEs
- All TEAEs Leading to Study Discontinuation
- All TEAEs leading to Deaths

8.2. Clinical Laboratory Evaluations

Listings of individual laboratory parameters by visit will not be presented. Significant laboratory results, as assessed by the Investigators, will be tabulated as AEs or SAEs and will appear in individual AE listings.

8.3. Vital Signs

Listings of vital sign results will not be presented. Significant vital sign values, as assessed by the Investigators, will be tabulated as AEs or SAEs and will appear in individual AE listings.

8.4. Physical Examination

Listings of individual physical examinations results will not be presented. Significant results, as assessed by the Investigators, will be tabulated as AEs or SAEs and will appear in individual AE listings.

8.5. Electrocardiograms (ECG)

Listings of individual ECG parameters (including HR, PR, QRS, QT and QT_CF) will not be presented. Significant results, as assessed by the Investigators, will be tabulated as AEs or SAEs and will appear in individual AE listings.

9. TABLES AND LISTINGS

Table 1: Data Summary Tables and Listings

Table Number	Table Title	Population
14.1	**Demographic Data**	
14.1.1	**Disposition**	
	Summary of Subject Dispositions	Safety Analysis Population
14.1.2	**Demographics**	
	Summary of Demographics and Baseline Characteristics	Safety Analysis Population
14.3	**Safety Data**	
14.3.1	**Displays of Adverse Events**	
14.3.1.1	Summary of Treatment Emergent Adverse Event	Safety Analysis Population
14.3.1.2	Summary of Treatment Emergent Adverse Event by System Organ Class and Preferred Term	Safety Analysis Population
14.3.1.3	Summary of Treatment Emergent Adverse Event by Preferred Term	Safety Analysis Population
14.3.1.4	Summary of Treatment Emergent Adverse Event by System Organ Class, Preferred Term and Maximum Severity	Safety Analysis Population
14.3.1.5	Summary of Treatment Emergent Adverse Event by System Organ Class, Preferred Term and Relationship to Study Drug	Safety Analysis Population
14.3.1.6	Summary of Treatment Emergent Serious Adverse Event by System Organ Class, Preferred Term	Safety Analysis Population

14.3.1.7	Summary of Treatment Emergent Serious Adverse Event led to discontinuation of study by System Organ Class, Preferred Term	Safety Analysis Population
Listing Number	**Listing Title**	**Population**
16.2	**Participant Data Listings**	
16.2.1	**Discontinued Subjects**	
	Participant Disposition	Safety Analysis Population
16.2.4	**Demographic Data**	
	Demographic and Baseline Characteristics	Safety Analysis Population
16.2.7	**Adverse Event Listing**	
16.2.7.1	Listing of All TEAEs	Safety Analysis Population
16.2.7.2	Listing of All TESAEs	Safety Analysis Population
16.2.7.3	Listing of All TEAEs Leading to Study Discontinuation	Safety Analysis Population
16.2.7.4	Listing of All TEAEs Leading to Deaths	Safety Analysis Population