Statistical Analysis Plan

Sponsor	Cassava Sciences, Inc.
Protocol Title:	An Open-Label, Long-Term Extension Study to Evaluate the Safety and Tolerability of Simufilam 100 mg Tablets in Participants with Mild to Moderate Alzheimer's Disease
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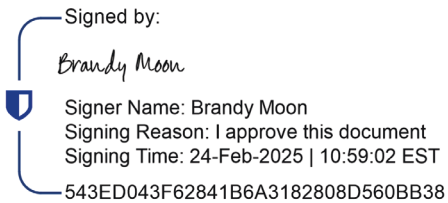
	Sign Name: 
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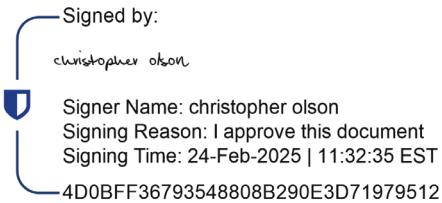
	Sign Name: 
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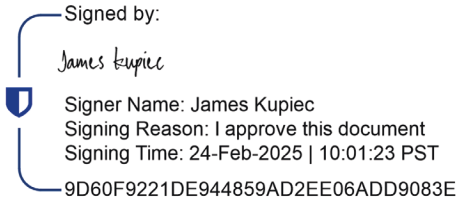
	Sign Name: 

Document History

SAP Version	Approval Date	Change	Rationale
0.1		Not applicable.	First draft
0.2		Response to the sponsor's comment on Draft version 0.1	Second draft
0.3		Response to sponsor's comments on Draft Version 0.2.	Third draft
1.0	22-Feb-2025	Finalized draft.	Finalized version

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ASA	American Statistical Association
BID	twice daily
BMI	body mass index
CDISC	Clinical Data Interchange Standards Consortium
CRF	case report form
CSR	clinical study report
DSMB	data safety monitoring board
ED	early discontinuation
EMA	European Medicines Agency
ET	early termination
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Conference on Harmonization
MedDRA	medical dictionary for regulatory activities
PT	preferred term
RSS	Royal Statistical Society
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan

Abbreviation	Definition
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TLF	table, listing and figure

1. Overview

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Cassava Sciences, Inc. protocol number PTI-125-10 (*An Open-Label, Long-Term Extension Study to Evaluate the Safety and Tolerability of Simufilam 100 mg Tablets in Participants with Mild to Moderate Alzheimer's Disease*), dated 10-Nov-2023 and protocol 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. Also, 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. The SAP will be finalized and approved prior to locking of the study database.

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.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of simufilam 100 mg tablets in subjects who have completed one of the two double-blind simufilam phase 3 studies.

2.2. Study Endpoints

2.2.1. 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.

3. Overall Study Design and Plan

3.1. Overall Design

As background for the statistical methods presented below, this section provides an overview of the study design and plan of study execution. The protocol is the definitive reference for all matters discussed in what follows.

This is a multi-national, multi-center, fixed-dose, 52-week, open-label extension study to evaluate the long-term safety and tolerability of simufilam 100 mg tablets in subjects who have completed one of the two double blind simufilam phase 3 studies. Subjects from either of the two double-blind simufilam phase 3 studies (PTI-125-06 or PTI-125-07) rollover into this open-label extension study, provided that all inclusion and none of the exclusion criteria are met.

Once participants enrolled in the study, visits to the research clinic will occur at Weeks 4, 16, 28, 40 and 52.

Safety will be evaluated by adverse event monitoring at every visit.

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.

No interim analysis is planned for this study.

3.2. Sample Size and Power

As the PTI-125-10 study is primarily focused on long-term safety of simufilam from rollover studies PTI-125-06 and PTI-125-07, no formal sample size was calculated.

3.3. Study Population

The study population is comprised of 1081 participants with mild-to-moderate AD. Participants are enrolled from approximately 141 clinical sites in the USA, Canada, the Republic of Korea, and Australia. For subjects electing to participate, the clinical and laboratory assessments from the Week 76 (PTI-125-06) or Week 52 (PTI-125-07) End-of-Treatment visit served as Baseline Visit assessments for the open-label study on Study Day 1.

3.4. Treatments Administered

All participants received simufilam 100 mg tablets BID.

3.5. Method of Assigning Subjects to Treatment Groups

This is an open-label, non-randomized study. All the participants received simufilam 100 mg tablets twice daily.

3.6. Blinding and Unblinding

All participants, investigators, and study personnel are aware of the treatment assignment and receipt of study drug during the conduct of the study, through database lock.

3.7. Schedule of Events

Table 1: Schedule of Events

Procedures	Baseline Visit (Study Day 1)	Week 4	Week 16	Week 28	Week 40	Week 52 ET/ED[3]	Week 53 to 54
Informed Consent	X						
I/E Criteria	X						
Adverse Events	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	
Brief Physical Examination	X	X	X	X	X	X	
Brief Neurologic Examination	X	X	X	X	X	X	
Height	X						
Weight	X	X	X	X	X	X	
Resting ECG	X	X		X		X	
Biochemistry, Hematology, Urinalysis	X	X		X		X	
HbA1c[3]	X			X[4]		X[4]	
C-SSRS[1]	X	X	X	X	X	X	
Drug Dispensation	X[2]	X	X	X	X		
Drug Accountability		X	X	X	X	X	
End of Study Follow-up Phone Call							X

1. On Study Day 1, as well as all remaining visits, the 'C-SSRS Since Last Visit' version will be administered.
2. The first dose of study drug is administered at the clinic to all subjects on Study Day 1 at least four hours after any prior dose and at least one hour before departure.
3. HbA1c collection will begin upon receipt of required supplies.
4. Week 28 and Week 52 HbA1c should only be collected in subjects with a Day 1 HbA1c.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will primarily use SAS (release 9.4 or higher). If the use of other software

is warranted, the final statistical methodology report will detail what software was used for what purposes.

Descriptive summaries of variables will be provided where appropriate. Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the category for each value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment group (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) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

This study is considered an exploratory study. Statistical tests will be interpreted in an exploratory sense only and will not be considered formal hypothesis tests.

4.2. Interim Analysis and Data Monitoring

No interim analyses are planned.

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 populations are planned for this study:

- **Safety Population (SAF):** The SAF analysis set includes all participants who received at least one dose of study treatment. This population will be used for all safety analysis.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last observation recorded before the first dose of treatment will be used as the baseline observation. The clinical and laboratory assessments performed at the Week 76 (PTI-125-06) or Week 52 (PTI-125-07) End-of-Treatment visit will serve as the baseline (Study Day 1) for this open-label extension study. In the event the End-of-Treatment visit and the Study Day 1 visit for the open-label extension study did not occur on the same date, the Medical Monitor was responsible for deciding whether any clinical and laboratory assessments needed to be repeated to

serve as baseline values for Study Day 1 depending upon the length of time between the two visits.

6.1.2. Adjustments for Covariates

No covariates are planned for this study.

6.1.3. Multiple Comparisons

No multiple comparisons are planned for this study.

6.1.4. Handling of Dropouts or Missing Data

Although every attempt will 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.

An incomplete start or stop date of an AE 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.

6.1.5. Pooling of Sites

No pooling of study centers is planned for this study.

6.1.6. Data Adjustments/Handling/Conventions

Only limited data required for analysis 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 listings. Data not subject to analysis according to this plan will not appear in any tables and listings.

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).

Ongoing AEs from the pivotal studies will be classified as TEAEs in the current study only if they increase in severity on or after the date of the first dose of study drug in the current study. Otherwise, they will be classified as medical history events.

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

For partial AE 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 is ongoing, then the date is assigned the first dose date thus the event will be considered as treatment-emergent; 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 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).

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

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 Patients/Subjects and Demographics

7.1. Disposition of Patients/Subjects and Withdrawals

A summary of the analysis sets includes the number and percentage of subject's rollover and in the safety population. All percentages will be based on the safety population.

The following will be summarized by treatment group:

- Number of participants who enrolled,
- Number and percentage of participants in safety 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.

7.2. Demographics and Other Baseline Characteristics

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 by treatment group using the descriptive statistics.

Height and weight will be measured at Study Day 1 and then the BMI will be calculated at Study Day 1. If height is missing in Study Day 1 then the pivotal studies screening visit height and Study Day 1 weight will be used for BMI calculation. Individual subject demographics and baseline characteristics will be provided in listings.

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.

These analyses will be conducted for the Safety populations.

7.3. Exposure and Compliance

8. Efficacy Analysis

8.1. Primary Efficacy Analysis

No applicable Primary Efficacy Analysis is planned.

8.2. Secondary Efficacy Analysis

No applicable Secondary Efficacy Analysis is planned.

9. Safety and Tolerability Analysis

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

Safety will be evaluated from reported AEs. No inferential statistical tests will be performed, unless otherwise specified.

For all safety and tolerability analyses, participants will be analyzed by the actual treatment.

All safety and tolerability data will be presented in 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 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 several 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:

- 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:

- 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

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

9.1.4. Summaries of Adverse Events

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.

10. Changes from Planned Analyses

Due to the early sponsor termination of PTI-125-10, the following analyses will no longer be tabulated/listed:

- Mean change in clinical laboratory values from baseline to Weeks 4, 28 and 52
- Mean change in vital signs (blood pressure [supine], temperature, pulse rate) from baseline to Weeks 4, 16, 28, 40, and 52
- Mean change in body weight from baseline to Weeks 4, 16, 28, 40, and 52

- Shifts in physical exam (PE) findings from baseline to Weeks 4, 16, 28, 40, and 52
- Shifts in neurological exam (NE) findings from baseline to Week 4, 16, 28, 40, and 52
- Mean change in ECG parameters from baseline to Weeks 4, 28, and 52
- Concomitant medications/treatments usage
- Shifts in the C-SSRS from baseline to Weeks 4, 16, 28, 40, and 52.
- Shifts in HbA1c values from baseline to Weeks 28 and Week 52. The analysis is done separately among subjects who were previously on placebo and simufilam in PTI-125-06 and PTI-125-07 phase 3 studies.

11. References

1. Protocol number PTI-125-10, An Open-Label, Long-Term Extension Study to Evaluate the Safety and Tolerability of Simufilam 100 mg Tablets in Participants with Mild to Moderate Alzheimer's Disease, dated 10-NOV-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/.

12. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (CRF page or listing number).

The following are planned summary tables for protocol number PTI-125-10. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

12.1. Demographic Data Summary Tables and Figures

Table 2: Demographic Data Summary Tables and Figures

Table Number	Population	Table Title/Summary
Table 14.1.1	Safety	Subject Disposition (Includes All Early Terminations)
Table 14.1.2	Safety	Demographics and Baseline Characteristics

12.2. Safety Data

Table 3: Safety Data

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

12.3. Planned Listing Descriptions

The following are planned data and patient/subject data listings for protocol number PTI-125-10.

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

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

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

Table 4: Planned Listings

Data Listing Number	Population	Data Listing Title / Summary
16.2 Subject Data Listings		
16.2.1 Subject Discontinuations/Completions		
Data Listing 16.2.1.1	Safety	Subject Disposition
16.2.4 Demographic Data and Other Baseline Characteristics		

Data Listing Number	Population	Data Listing Title / Summary
16.2 Subject Data Listings		
Data Listing 16.2.4.1	Safety	Demographic and Baseline Characteristics
16.2.7 Adverse Event Listings (by Patient/Subject)		
Data Listing 16.2.7.1	Safety	Treatment Emergent Adverse Events