Study Title:

A Phase 2b, Randomized, Double-blind, Placebo-controlled, Multiple Dose, Biomarker and Safety Study of PTI-125 in Mild-to-moderate Alzheimer's Disease Patients

project:

PTI-125-02

(NCT04079803)

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Statistical Analysis Plan

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Approval

This Statistical Analysis Plan document has been reviewed and approved by the following personnel:

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Approval

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Table of Contents

List of Abbreviations

AD	Alzheimer's Disease
AE	Adverse Event
ALT	Alanine Transaminase
ALP	Alkaline Phosphatase
ANCOVA	Analysis of Covariance
APOE	Apolipoprotein
AST	Aspartate Transaminase
AUC	Area Under the Curve
BID	bis in die (two times a daily)
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CI	Confidence Interval
Cmin	Minimum blood Plasma Concentration
Cmax	Maximum Plasma Concentration
CRO	Contract Research Organization
CS	Compound Symmetry
CSF	Cerebrospinal Fluid
CSI	Cassava Sciences, Inc.
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CSV	Comma-Separated Values
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
Emax	The maximum response attributable to the drug
EOD	End of Drug
EOS	End of Study
FAS	Full Analysis Set
FDA	Federal Drug Association
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
IE	Inclusion/Exclusion Criteria
Kg	Kilogram(s)
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram(s)
mg/Dl	Milligrams per deciliter

Ml	Milliliter(s)
Mm	Millimeter(s)
MMSE	Mini-Mental State Examination
MmHg	Millimeters of mercury
PK	Pharmacokinetics
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
SD	Standard Deviation
SE	Standard Error
SI	International System of Units
SOC	System and Organ Class
SP	Safety Population
TEAE	Treatment-emergent AE
TLF	Tables, Listings, and Figures
VS	Vital Signs
VC	Variance Component
WHO-DD	World Health Organization Drug Dictionary

Introduction

Purpose

The purpose of this Statistical Analysis Plan (SAP) is to provide a thorough description of statistical methods and presentation of the study data to be used for the analysis of data generated from the clinical trial description in protocol Version dated June 28, 2019 : "A Phase 2b, Randomized, Double-blind, Placebo-controlled, Multiple Dose, Biomarker and Safety Study of PTI-125 in Mild-to-Moderate Alzheimer's Disease Patients". Results from the analyses completed will be included in the final clinical study report for PTI-125-02, and may also be utilized for regulatory submissions, manuscripts, or other clinical development activities.

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

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

The SAP will be finalized and approved prior to unblinding of any study data. 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. Arbitrary treatment group assignments must be randomly linked to subjects, effectively rendering any output of programs meaningless.

For the reasons stated here the conduct of the study in the field is considered to be independent of any study outcome that might materialize upon enactment of the currently proposed statistical plan.

1. Study Objectives/Hypothesis Testing

1.1 Study Objectives

The primary objectives for this study are to:

- Assess the safety of PTI-125 following 1-month, repeat-dose oral administration in mild-to-moderate Alzheimer's Disease (AD) patients, 50-85 years of age, with 16 ≤ MMSE ≤ 26.
- Assess the effect on biomarkers of PTI-125 following 1-month, repeat-dose oral administration in mild-to-moderate AD patients, 50-85 years of age, with 16 ≤ MMSE ≤ 26.
- Assess the effect on cognition of PTI-125 following 1-month, repeat-dose oral administration in mild-to-moderate AD patients, 50-85 years of age, with 16 ≤ MMSE ≤ 26.

The second objective is to replicate the effects on biomarker shown in the previous open label 1-month study.

The third objective is to investigate a dose response of PTI-125.

1.2 Study Endpoints

1.2.1 Primary Endpoint

The primary endpoint for this study will be to evaluate the change in value of specific cerebral spinal fluid (CSF) biomarkers from the second screening to Day 28 between each dose group and placebo.

1.2.2 Secondary Endpoint

- The secondary endpoint for this study will be to evaluate the change in CSF biomarkers from the second screening to Day 28 within the study treatment groups.
- The secondary endpoint for this study will be to evaluate the change in Cambridge Cognition testing from the Day 1 to Day 28 between each dose group and placebo
- .
- The secondary endpoint for this study will be the dose-response of the study drug.

1.2.4 PK Endpoint

The PK endpoint for this study is the C_{min} value from the blood samples taken on Days 7, 14 and 28.
CSF to plasma ratio will be determined using the Day 28 CSF and plasma samples.

1.2.5 Safety Endpoint

Adverse events, vital signs, clinical laboratory tests and ECG test results.

1.3 Hypothesis to be Tested

The primary endpoint of CSF biomarker will be analyzed by ANCOVA at a significant level of 5% to test the null hypothesis:

$H_0: \mu_i = \mu_j$
$H_1: \mu_i \neq \mu_j$

For all $i \neq j$, where μ_i indicates the mean observation for a particular CSF biomarker endpoint for the i^{th} treatment.

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2.0 Background

2.1 Study Design

This Phase 2b study is a randomized, double-blind, placebo-controlled trial of PTI-125 oral tablets given to patients with mild to moderate Alzheimer's Disease. Sixty patients are expected to be enrolled in the trial and randomized to one of the three cohorts. Cohorts will receive placebo or PTI-125 at 50 or 100 mg twice a day.

Two screening visits will be scheduled within 30 days of start of the study (Figure 1) Subjects meeting the initial screening criteria will return for a cerebrospinal fluid (CSF) draw at a second screening visit. A second CSF sample will be collected at day 28 visit for CSF biomarkers as well as analysis of PTI-125. Cambridge Cognition testing will be conducted at the second Screening visit, Day 1 and at the Day 28 visit.

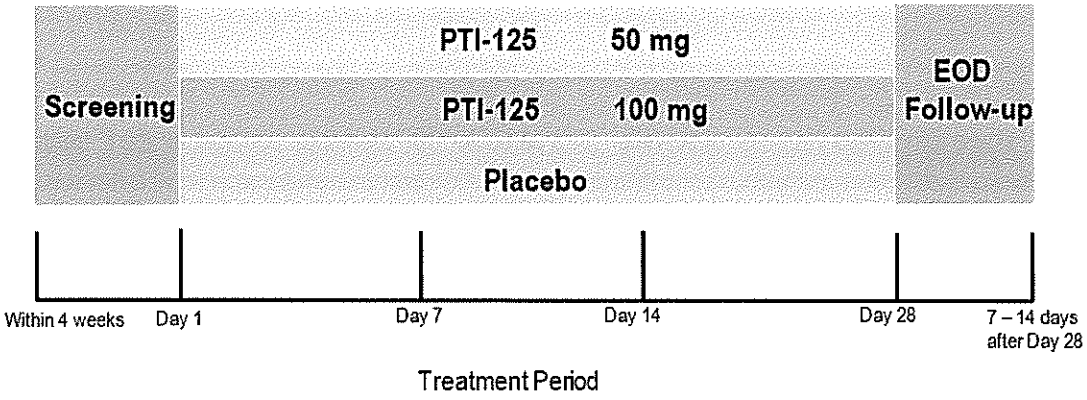
On Screening visit 1 and Day 28, patients will be assessed for suicidality via the C-SSRS.

Subjects will report to the clinic on the morning of Day 1 and the following will be conducted: Cambridge Cognition testing, a full physical exam, an ECG and a blood draw for clinical labs and biomarkers. Subjects will be monitored for Adverse Events (AE) and Vital Signs (VS) will be taken through 2 hours post- dosing. Subjects will return to the clinic on Days 7, 14 and 28 for blood draws for clinical laboratory testing, safety assessments of vital signs, ECGs.

PK blood samples will be obtained prior to the first dose on Day 7, Day 14, and Day 28 for C_{min} values. On Day 28, there will be a CSF draw after the last dose, and an additional PK blood sample will be obtained after this CSF draw for calculation of CSF/plasma ratio.

Blood samples for testing in PTI-125Dx, the companion diagnostic/biomarker, mTOR activation and other potential blood-based biomarkers will be drawn on Day 1 and Day 28. The Day 14 blood sample will also be used for APOE genotyping. A CSF sample collection will be performed on Day 28 for neurogranin, neurofilament light chain, total tau, pTau (T181), Aβ42, Aβ40, YKL40, IL-6, IL-1β, TNFα and other potential CSF biomarker assays as well as bioanalysis of PTI-125.

Figure 1. Study Design Schema



2.2 Inclusion/Exclusion Criteria

The inclusion and exclusion criteria are defined in the final protocol (Section 5.2) and apply to all subjects who consent to the study.

2.3 Treatment Groups

2.3.1. Randomization and Blinding

On Day 1, prior to dosing, 60 Subjects will be randomized at a 1:1:1 ratio to the following 3 treatment arms:

1. PTI-125: 50mg twice daily
2. PTI-125: 100 mg, twice a day
3. Matching Placebo, twice daily

Randomization will be performed using an Interactive Web Response System (IWRS).

Randomized treatments will be assigned by subject numbers in a randomly generated numeric sequence only after the subject has met all the I/E criteria.

As this is a double-blind, placebo-controlled study, the randomization code shall be blind to study subjects, investigators, clinical staff or study monitors until all subjects have completed therapy and the database has been finalized and locked.

2.3.2 Treatment Compliance

The investigator will be responsible for monitoring the receipt, storage, dispensing and accounting of all study medications. A summary of the total amount of medication taken by patient as per total daily dose and number of tablets per day should be provided by treatment groups.

2.4 Study Population

Approximately 60 subjects (male and female) with mild-to-moderate AD will be enrolled in the study. Dropouts may be replaced at the discretion of the Sponsor.

2.5 Study Drug and Dosing

PTI-125 tablets and placebo tablets are packaged in identical bottles affixed with a blinded label that includes the protocol number and treatment assignment number on the respective bottle. Placebo or PTI-125 will be supplied by Cassava Sciences (CSI) as coated tablets in 20-count bottles.

Study drug will be administered at least 1 hour before or after a meal twice a day. A dose can be up to 4 hours late, but if a dose is missed, the next dose should not be doubled.

2.6 Sample Size

Approximately 60 subjects will be enrolled in this study. Sample size was determined by estimating the intrasubject variability for log-transformed data from previous studies of new chemical entities. (in reference to Protocol section 10.6)

2.7 Schedule of Time and Events

Approximately sixty (60) subjects will be enrolled into the study and randomized to one of three cohorts [(Placebo or PTI-125 at 50 or 100 mg b.i.d. (n=20 per group)].

There will be two screening visits within 30 days of start of the study. Subjects that meet the randomization criteria will return to the clinic for subsequent visits at Days 1, 7, 14 and 28.

The schedule for assessments and timing of events is presented in Table 1

Table 1. Schedule of Time and Events

PROCEDURE	SCREEN 1 (Days -29 to Day -1)	SCREEN 2 (Days -28 to Day 0)	DAY 1 Time=0	DAY 7	DAY 14	DAY 28
Informed consent	X					
Medical and medication histories	X		X			
ECG	X		X		X	X
Vital signs	X		X	X	X	X
Physical examination	X		*	*	*	X
FSH Test**	X					
Biochemistry, hematology, urinalysis	X		X	X	X	X
MMSE	X					X
HCV, HBsAg & HIV screen	X					
Urine drug screen	X					
Drug administration			X	X	X	X
Blood sample collection for PK analysis				X	X	X
Adverse Events			X	X	X	X
Blood draw for biomarkers and one time only, APOE genotyping			X			X
Cambridge Cognition testing		X	X			X
C-SSRS	X					X
CSF draw		X				X

* Listen to heart and lungs ** If female and last natural menses < 24 months or uncertain

3.0 Populations of Analysis Sets

All subjects who receive study medication will be included in analyses for safety.
All subjects for which data is available for both Screening 2 and Day 28, will be included in the biomarker analysis
All subjects for which data is available for Day 1 and Day 28 will be included in the cognition analysis.

4.0 Data Analysis Considerations

4.1. Analysis Populations

There will be two analysis populations defined for this study.

4.1.1. Full Analysis Set Population (FAS)

The Full Analysis Set population includes all subjects who receive at least one dose of study treatment and have evaluable efficacy records at baseline and post-baseline visits. The Full Analysis Set population will be used for all efficacy analyses. Subjects will be analyzed as treated.

4.1.2. Safety population (SP)

The Safety population will include all subjects who receive at least one dose of the study treatment.
All safety analyses will be based on the Safety population. Subjects will be analyzed as treated.

4.2. Covariates and Subgroups

4.2.1. Planned Covariates

Covariates for analysis of key efficacy data will be identified prior to study unblinding

4.2.2. Planned Subgroups

Subgroups for analysis of key efficacy data will be identified prior to study unblinding

4.3 Management of Analysis Data

4.3.1 TLFs Presentation

All tables, listings and figures will be presented in landscape format. SAS version 9.4 will be used for reporting this study and all outputs will be sent to CSI as electronic files in Rich Text Format (RTF) format documents.

4.3.2 Definition of Analysis Timepoints

The following analysis timepoints will be considered for this study:

Screening/ Baseline (-30 to Day 1)
All screening evaluations are to be considered within 30 days prior to the first dose of PTI-125 (Day 1).
Baseline is defined as the last non-missing value on or before the first treatment date.

PTI-125 treatment evaluation period (Day 1 to Day 28)
Subjects will come to the clinic for safety assessment on Day 1, Day 7, Day 14 and Day 28, prior to the morning dose administration.

4.3.3 Data Handling Rules for Unscheduled Visit

Unscheduled tests will be included with the time of the nearest regularly scheduled test. If there is a scheduled test and one or more unscheduled tests assigned to the same time point, the most conservative test (i.e., a test with the lowest or highest results) will be used. Repeated tests will be included only if they reflect abnormal (low or high) results and the corresponding original results are normal.

4.3.4 Missing Data

Missing data will not be imputed for the purpose of this analysis. All data recorded on the electronic case report form (eCRF) will be included in data listings that will accompany the clinical study report, as applicable.
For qualitative parameters, a category with the number of patients with missing values will be presented where applicable.
Missing data imputations for Adverse Events will be included in the TEAE. Instead, the data will be presented in the AE listings.

4.3.5 Handling of Early Termination Visit Information

If a subject 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.

4.36 Pooling of Investigational Sites

The data from all study centers will be pooled together for all planned analyses.

4.3.7 Coding Conventions for Events, Medical History and Medications

All adverse events and medical history indication will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) (version 22.1)

All Concomitant medications will be coded using World Health Organization (WHO) Drug Global C3 (version Mar 1, 2019).

4.3.8 Analysis Software

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

4.3.9 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). The CANTAB cognitive test results will be provided to Axiom Biostats post unblinding of the database in comma-separated values (CSV) format.

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 1.4 and SDTM Implementation Guide (SDTM IG) version 3.2 will be used.
- ADaM Model 2.1 and ADaM Implementation Guide (ADaM IG) version 1.1 will be used.

Dropouts may be replaced during the study, will be included in the data analysis to the extent that evaluable data is present.

4.4 Planned Analyses

4.4.1 Statistical Summaries: Descriptive and Inferential

All statistical tests will be two-sided and a difference resulting in a p-value of less than or equal to 0.05 will be considered statistically significant.

All p-values will be rounded to and displayed in four decimals. If a p-value less than 0.0001 occurs, it will be shown in tables as <0.0001.

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

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

5.0 Summary of Baseline Characteristic Data

5.1 Subject Disposition

Subject disposition will be summarized by treatment and will include:

- The number of subjects randomized
- The number of subjects in the FAS set
- The number of subjects in the safety set
- The number and percentage of subjects who completed or discontinued the study at each study site (based on actual treatment, not randomization)

All percentages will be based on the number of subjects randomized. A subject level data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

5.2 Protocol Deviations

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

5.3 Demographics and Baseline Characteristics

The demographics consist of age (year), sex, race, and ethnicity. The baseline characteristics consist of baseline height (cm), baseline weight (kg), and baseline body mass index (BMI) (kg/m2). Body mass index is calculated as (body weight in kilograms) / (height in meters)2.

Subject demographic data and baseline characteristics will be tabulated and summarized descriptively by treatment group. The demographic data and baseline characteristics will be summarized for the FAS population.

Individual subject demographics and baseline characteristics will be provided in listings.

5.4 Medical Histories

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (Version 22.1).
Subject medical history data including specific details will be presented in a listing.

5.5 Concomitant Medications

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD) Global C3 (Version Mar 1, 2019).

All medication data will be presented in listings;

5.6 Treatment Compliance

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 subject's participation in the study.

- Treatment compliance will be summarized by treatment group.
- Treatment compliance data will be presented in a data listing.

6.0 Efficacy Analysis

All the efficacy analyses will be performed using the FAS population.

6.1 Efficacy Endpoints

The efficacy endpoints are summarized in Table 2.

Table 2. Summary of Efficacy Parameters

Parameter	Method of Determination / Derivation
Primary Efficacy Endpoint	
Change from Screening Visit 2 of the specific CSF biomarker on Day 28	Change = Day 28 – Screening Visit 2
The Cambridge Cognition tests results	NA

6.2 Efficacy Analyses

6.2.1 Primary Efficacy Analysis

CSF Biomarkers

The baseline, post baseline, and change from baseline values will be summarized by treatment group based on the FAS population. The change from baseline on Day 28 will be analyzed by using a General Linear Model for the ANCOVA. The model will include the change from baseline as the dependent variable, the fixed effect of treatments, and baseline CSF biomarkers measurement as covariate. The means, Least Squares (LS) means, a 2 sided 95% confidence intervals (CI) for each LS means, differences between LS means, a 2 sided 95% CIs for each difference and the p-values from model effects will be reported in the summary table.

6.2.2 Secondary Efficacy Analysis

CSF Biomarkers at Screening Visit 2 and Day 28 will be compared by using the two tailed paired t-test per each treatment group (Placebo, PTI-125 50 mg, and PTI-125 100 mg). The analysis will be performed based on the FAS population. The means, differences between means of Screening Visit 2 and Day 28, a 2 sided 95% CIs for the difference and the p-values from the t-test will be reported in the summary table.

Cambridge Cognition Test

Results will be summarized for subjects by treatment group. The summary and statistical analysis will be conducted using FAS population. The change from baseline on Day 28 will be analyzed by using a General Linear Model for the ANCOVA. The model will include the change from baseline as the dependent variable, the fixed effect of treatments, and baseline Cambridge cognition measurement as covariate. The means, Least Squares (LS) means, a 2 sided 95% confidence intervals (CI) for each LS means, differences between LS means, a 2 sided 95% CIs for each difference and the p-values from model effects will be reported in the summary table.

6.2.3 Dose Response Analysis

Nonlinear E_{max} model will be used in dose-response analysis. The model has the following form:

$$R_i = E_0 + \frac{D_i^N \times E_{max}}{D_i^N + ED_{50}^N} + \varepsilon_i$$

Where:

i = patient;
R_i = The value of response for patient i (ex. Defined to be "Change form Baseline in $A\beta_{42}$ at Day 28" should be repeated for the remaining CSF Biomarkers);
D_i = Concentration of the drug in the plasma of the patient i at Day 28;
E_0 = Basal response, when the concentration of the drug is zero or minimal;
E_{max} = The maximum response attributable to the drug;
ED_{50} = The concentration that produces half of maximum response;
N = The slope measures the change in response by moving from one concentration level to another;
ε_i = The random error term for patient i – i.i.d and follows normal distribution with mean – 0 and variance.

Treatment group response will be predicted by applying the E_{max} model which intrinsically has 4 parameters to estimate (E_0, E_{max}, ED_{50}, N). This can be performed with "Proc NLIN" procedure in SAS by arbitrary specifying starting estimates for these parameters by treatment groups.

To assure optimal convergence of the procedure, the following starting estimates will be applied:

	Placebo	PTI-125 50mg	PTI-125 100mg
E_0	0	Minimum response from observed data	Minimum response from observed data
E_{max}	100	Maximum response from observed data	Maximum response from observed data
ED_{50}	5	1	1
N	1	1	1

Results will be summarized and presented graphically by treatment groups based on the FAS. Parameter estimates will be presented together with 95% CIs.

7.0 Safety Analysis

All the safety parameters presented below will be descriptively presented for each treatment level using Safety population in this study. No comparison will be done between levels, therefore no statistical tests will be reported for the safety parameters.

7.1 Adverse Events

Adverse event reports will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA Version 22.1) and presented by system and organ class (SOC) and preferred term.
The severity of all AEs will be characterized and classified into one of three defined categories as Mild, Moderate and Severe.

The causality of all AEs to the study drug will be classified into one of three defined categories as Unlikely, Possible and Probable.

A Treatment-emergent AE (TEAE) is defined as an event which occurred following the first dosing of study treatment, or that started prior to the first dosing and worsened during the treatment.

An overall summary of AEs during the trial will be presented by treatment level. This summary will include the number and percentage of patients with any AEs, a TEAE, a serious TEAE, a related TEAE, a serious related TEAE, a TEAE leading to discontinuation and a TEAE leading to death.

The number and percentage of patients reporting TEAEs will also be presented by treatment level. Frequency tables of TEAEs will be presented by treatment level, MedDRA system organ class and preferred term and will include the number and percentage of patients report the event. The same summary tables will also be presented for serious TEAEs, related TEAEs, serious related TEAEs, TEAEs leading to discontinuation and TEAEs leading to death.

7.2 Vital Signs

The vital signs include blood pressure, temperature, pulse and respiratory rate. For each scheduled visit, summary statistics will be provided (study population size, mean, SD, minimum, median, and maximum) for each vital sign parameter, by treatment level. Summary statistics for change from screening values will also be presented.

7.3 ECG

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

7.4 Laboratory Data

The clinical laboratory assessments include Hematology, biochemistry and Urinalysis.
Laboratory data will be converted to International System of Units (SI units), using commonly available conversion factors. Summary statistics will be based on the converted values. The data listings will contain both the original as well as the converted values.

Descriptive statistics (study population size, mean, SD, minimum, median, and maximum) for each laboratory test and their change from screening values will be presented by treatment group for each scheduled visit.

7.5 Physical Examination

Full physical examination data will be listed by treatment level and patient only.

8.0 Listing of Listings, Tables and Figures

The list of data displays planned for presentation in the study report of Protocol Number PTI-125-02 will be provided in the document "Axiom – Cassava Sciences – PTI-125-02 - Mock TLFs". The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study but are intended to show the general layout of the Tables, Listings and Figures that will be included in the final report. Tables, Listings and Figures are numbered following the International Conference on Harmonization (ICH) structure. Table headers, variables names and footnotes might will be modified as needed following a review of the blinded data or following data analyses. All tables, listings and figures will be generated using SAS® Version 9.4 or higher.

Change Control

Client Version	Section changed	Details of change
Live v1.0	Initial Document	N/A