Worldwide Clinical Trials Controlled Quality Management Document		
WORLDWIDE CLINICAL TRIALS	Sponsor:	TB Alliance
	Protocol Number:	Pa-824-CL-011
STATISTICAL ANALYSIS PLAN – PHASE 1		

Statistical Analysis Plan

An Open-label, Randomized, Four-period Crossover Study in Two Panels of Healthy Adult Participants to Assess the Relative Bioavailability, Food Effect, and Dose-dependence of Single-Dose Immediate-Release and Single-dose Dispersible Formulations of Pretomanid

Protocol Number: *Pa-824-CL-011*

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Previous SAP Versions

Not Applicable

SAP Amendments Before Database Lock

Version	Issue Date	Section	Revision / Addition	Rationale
	Not Applicable			

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1 INTRODUCTION

This document details the planned statistical analyses for TB Alliance, protocol "Pa-824-CL-011" study titled "An Open-label, Randomized, Four-period Crossover Study in Two Panels of Healthy Adult Participants to Assess the Relative Bioavailability, Food Effect, and Dose-dependence of Single-Dose Immediate-Release and Single-dose Dispersible Formulations of Pretomanid". The proposed analyses are based on the contents of the final version of the protocol (dated 06-Dec-2019).

This is a single-dose, open-label, randomized, four-period, four-treatment, crossover study in healthy adult subjects. Each panel of 24 subjects will be randomized according to the same 4-sequence, 4-period Williams design, in which each participant will receive four single-dose treatments. Subjects in Panel 1 will receive all treatments after consuming an FDA standard high-fat, high-calorie breakfast following an overnight fast of at least 10 hours. Subjects in Panel 2 will receive all treatments directly following an overnight fast of at least 10 hours. The two panels will be investigated concurrently. The maximum duration of the study from screening to study exit will be approximately 54 days.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to assess the relative bioavailability of the single-dose dispersible formulation intended for pediatric treatment, using the 200-mg single-dose immediate-release formulation as the reference.

2.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To determine the food effect for each of the formulations.
- To assess the effect of dose on the bioavailability of the dispersible pediatric formulation under fed and fasted conditions.
- To evaluate the taste perception of the dispersible pediatric formulation under fed and fasted conditions.
- To evaluate the short-term safety and tolerability for each of the formulations under fed and fasted conditions.

3 ENDPOINTS

3.1 Safety Endpoints

Safety assessments will include physical examinations, vital sign measurements, clinical laboratory evaluations, electrocardiograms (ECGs), and reported or observed adverse events (AEs). Subjects will be monitored continuously for any AEs from the signing of the informed consent through the end of the study.

3.2 Pharmacokinetic Endpoints

Full pharmacokinetic (PK) profiles of pretomanid will be determined up to 96 hours after each intake of pretomanid. Blood samples for analysis of pretomanid concentrations will be drawn just before drug intake (pre-dose), and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours post dose (15 samples per dose).

Primary PK measures include T_{max}, C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$. Secondary PK measures include the ratio of $AUC_{0\text{-}t}$ to $AUC_{0\text{-}inf}$, $T_{1/2}$, Kel, Cl/F and Vd/F.

4 SAMPLE SIZE

Two panels of healthy male and female subjects (24 subjects per panel) will be dosed in this study. The sample size is not based on statistical considerations. The number of subjects planned for enrollment is considered sufficient to achieve the study objectives.

5 RANDOMIZATION

This is an open-label study without treatment blinding. Subjects will be randomly allocated to a panel by clinic staff, and the two panels will be investigated concurrently. Subjects in each panel (Panel 1 = Fed, Panel 2 = Fasted) will be randomized to a treatment sequence based on a 4-sequence, 4-period Williams design prepared by the independent statistician.

Table 1: Treatment Schedule

Sequence (n=24 subjects per panel)	Treatment Periods			
	Period 1	Period 2	Period 3	Period 4
ABCD	A	B	C	D
BDAC	B	D	A	C
CADB	C	A	D	B
DCBA	D	C	B	A

Treatment A (reference) = 200 mg given as a single 200 mg tablet (using the immediate release formulation), orally administered.

Treatment B (test) = 200 mg given as four 50-mg tablets (using the dispersible pediatric formulation), orally administered.

Treatment C (test) = single 50-mg dispersible tablet, orally administered.

Treatment D (test) = single 10-mg dispersible tablet, orally administered.

6 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be absolutely definitive and the final Clinical Study Report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

6.1 Analysis Sets

Subjects excluded from the analysis sets and the reason for their exclusion will be listed in Appendix 16.2 of the CSR.

6.1.1 Randomized Set

The Randomized Set includes all subjects to whom a treatment was randomly assigned.

6.1.2 Safety Analysis Set

The Safety Analysis Set includes all subjects who received any dose of study drug.

6.1.3 Pharmacokinetic Analysis Set

All evaluable subjects completing at least one treatment period will be included in the

PK analysis set.

6.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

6.2.1 Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labeled “Multiple Race” in the summary tables. The listings will reflect the original selected categories.

6.2.2 Baseline

For variables that will be summarized by treatment, the baseline for each period is defined as the last non-missing value (either scheduled, unscheduled or repeat) that is collected before dosing, but after check-in for the relevant period.

For variables that will be summarized overall, baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) that is collected before the subject receives the first dose of study drug.

6.2.3 Early Terminations Assessments

Early withdrawal (EW) assessments will be tabulated with End of Study (EOS).

6.2.4 Duration / Study Day / Time

Study day will be calculated as the number of days from first dose of study drug.

- date of event – date of first dose of study drug + 1, for events on or after first dose
- date of event – date of first dose of study drug, for events before first dose.

6.2.5 Conventions for Missing and Partial Dates

It is not expected that there will be any missing dates, however in the rare case that an Adverse Event (AE) start date or time is missing and it is unclear whether the AE is treatment emergent or not then a conservative approach will be taken and it will be assumed that the AE occurred after first dosing.

All dates presented in the individual subject listings will be as recorded on the Electronic Case Report Form (eCRF).

6.2.6 Inexact Values

In the case where a safety laboratory variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

6.2.7 Unscheduled Visits

Only scheduled post-baseline assessments will be tabulated. Post-baseline repeat / unscheduled assessments will not be summarized but will be listed in the relevant appendices to the CSR.

6.2.8 PK Parameters

6.2.8.1 Concentration-Time Data

Blood samples for analysis of pretomanid concentrations for each panel (Panel 1=Fed; Panel 2=Fasted) will be drawn just before drug intake (pre-dose), and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours post dose (15 samples per dose).

Concentration-time data will be tabulated by panel, treatment, and nominal time using descriptive statistics including: sample size (n), arithmetic mean (mean), standard deviation (SD), percentage coefficient of variation (% CV), geometric mean, median, minimum (min), and maximum (max). For presentation of the individual data and summary statistics, concentrations below the limit of quantitation (BLQ) will be set to zero. Geometric means will be presented as NC (not calculated) if BLQ values are present in the concentration-time dataset.

Individual subject and mean plasma concentration-time data will be presented graphically on linear and semi-logarithmic scales by panel. Mean data will be plotted using nominal sample times, and individual data will be plotted using actual times.

6.2.8.2 PK Parameters

Concentration-time data for pretomanid will be analyzed by noncompartmental methods using Phoenix™ WinNonlin® (Version 8.1, Certara, L.P.) in conjunction with the internet-accessible implementation of Pharsight® Knowledgebase Server™ (PKSO; Version 4.0.4, Certara, L.P.).

During the pharmacokinetic analysis, concentrations below the limit of quantitation (BLQ) up to the time of the first quantifiable concentration will be treated as zero. Embedded (values between 2 quantifiable concentrations) and terminal BLQ concentrations will be treated as "missing". Actual sample times relative to the time of dose administration will be used in the PK analysis. If actual times are missing, nominal times may be used.

The following PK parameters will be calculated for pretomanid for each panel:

Parameter	Definition
C_{max}	Maximum plasma concentration, determined directly from individual concentration-time- data
T_{max}	Time of the maximum plasma concentrations
C_{last}	Last quantifiable plasma concentration determined directly from individual concentration-time data
T_{last}	Time of the last quantifiable plasma concentration
AUC_{0-t}	Area under the plasma concentration-time curve from time-zero to the time of the last quantifiable concentration (C_{last}), as calculated by the linear trapezoidal rule
AUC_{0-inf}	Area under the plasma concentration-time curve from the time of dosing extrapolated to infinity, calculated as: $AUC_{0-inf} = AUC_{0-t} + C_{last}/\lambda_z$, where λ_z is the apparent terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration versus time curve
AUC_{Extrap}	The percentage of AUC_{0-inf} based on extrapolation, calculated as: $[1 - (AUC_{0-t}/AUC_{0-inf})]* 100$
λ_z (K_{el}, Lambda z)	The apparent elimination rate constant λ_z will be calculated as the negative of the slope of the linear regression through the terminal log-linear segment of the plasma concentration-time curve (additional criteria are summarized below)
$T_{½}$	The observed terminal elimination half-life, calculated as: $T_{½} = \ln(2)/\lambda_z$

Parameter	Definition
CL/F	The apparent total plasma clearance after an oral dose, calculated as: $CL/F=Dose/AUC_{0\text{-}inf}$, where F is the bioavailability,
V_z/F	The apparent volume of distribution after an oral dose, calculated as: $V_z/F=Dose/(AUC_{0\text{-}inf} \times \lambda_z)$, where F is the bioavailability,

Lambda-z (λ_z) Acceptance Criteria

The following criteria will be used to report lambda-z and related parameters:

- At least 3 quantifiable concentration-time points should be used in the regression
- C_{max} or data prior to C_{max} should not be included in the regression
- Adjusted R^2 should be ≥ 0.8000

If these acceptance criteria are not met, lambda-z and descriptive parameters such as the time range for the regression, adjusted R^2, etc. will be retained in a parameter listing for informational purposes. Lambda-z will be excluded from summary statistics and from subsequent PK calculations; parameters calculated using lambda-z (e.g. $t_{1/2}$, $AUC_{0\text{-}inf}$, CL/F, and V_z/F) will be reported as ND (not determinable).

If lambda-z acceptance criteria are met and $AUC_{0\text{-}inf}$ is estimable, the following criteria are used to report $AUC_{0\text{-}inf}$:

- The percentage of $AUC_{0\text{-}inf}$ based on extrapolation should be <30.0%.

If the percentage of $AUC_{0\text{-}inf}$ based on extrapolation is 30.0% or greater, $AUC_{0\text{-}inf}$ and AUC_{Extrap} will be retained in a PK parameter listing for informational purposes; these parameters will be excluded from summary statistics, subsequent PK calculations (e.g. CL/F, V_z/F), and statistical analysis (e.g. ANOVA).

PK parameters will be summarized separately for each panel by treatment using the following descriptive statistics: n, mean, SD, median, min, max, CV%, geometric mean, and geometric mean CV%.

6.2.8.3 Emesis

Subjects that experience emesis within 4 hours of dosing will be excluded from the PK analysis for the period during which the emesis occurred.

6.2.8.4 Unable to Complete FDA Standard Breakfast

Subjects in Panel 1 that are unable to complete the high-calorie, high-fat FDA breakfast will be excluded from PK analysis during which the incomplete breakfast occurred.

6.2.8.5 Quantifiable Predose Concentrations

If a quantifiable predose plasma concentration is identified, the following procedures will be followed:

- If the quantifiable predose concentration is less than 5% of the respective C_{max}, the value will be included in the concentration-time, PK, and statistical analysis without adjustment,
- If the predose concentration is greater than 5% of the respective C_{max}, the concentration-time data for the subject in question will be excluded from concentration-time analysis (mean and individual plots; concentration time tables), PK and statistical analyses. Quantifiable predose concentrations that are greater than 5% of the respective C_{max} will be retained in the concentration-time listing. If there are several instances of predose concentrations being greater than 5% of the respective C_{max} value, additional tables or statistical tests may be warranted and will be discussed with the Sponsor prior to final PK analysis.

6.3 Conventions

All clinical data listings, summaries, figures and statistical analyses will be generated using SAS (Version 9.4 or higher)[1].

Summaries of the clinical data will be presented by treatment panel and treatment group or overall.

PK data listings, summaries, figures, and statistical analyses will be generated using Phoenix™ WinNonlin® (Version 8.1 or higher)[2] or SAS (Version 9.4 or higher)[1]. PK concentration data will be summarized by panel and treatment at each nominal sample time. PK parameter data will be summarized by panel and treatment.

Treatment panel labels will be displayed as follows:

Panel 1	Panel 2
(Fed)	(Fasted)

Treatment group labels will be displayed as follows:

Pretomanid 200 mg IR Tablet	Pretomanid 4 x 50-mg Dispersible Tablets*	Pretomanid 50-mg Dispersible Tablet	Pretomanid 10-mg Dispersible Tablet

IR = Immediate Release; *Dispersible Pediatric Formulation.

Listings will be sorted in the following order: subject number, treatment panel, treatment sequence parameter, and visit unless otherwise stated. All data will be listed.

For clinical data, continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum.

PK data (concentration-time data and PK parameters) will be summarized by the number of non-missing observations (n), mean, standard deviation (SD), median, minimum (min), maximum (max), and coefficient of variation (CV%), calculated as (SD/Mean)*100. In addition, the geometric mean and geometric CV%, calculated as SQRT[exp(SD^2 of log transformed data)-1]*100, will be reported for C_{max} and AUCs.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the analysis set unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

6.3.1 Decimal Places

Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g. standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

For PK data, individual concentrations and PK parameters will be reported to 3 significant figures. Nominal and relative times will be presented to 3 significant figures. For summary statistics, n will be reported as a whole number; mean, standard deviation, median, minimum, maximum, CV%, geometric mean, and geometric mean CV% will be reported to the same precision as for individual data. For results from the statistical comparisons, least squares (LS) means and geometric LS means will be presented to 3 significant figures, p-values will be reported to 4 decimal places, percent ratios of the geometric LS means and associated 90% confidence intervals will be reported to 2 decimal places.

6.4 Subject Disposition

Subject disposition will be summarized as follows:

- The number of subjects completing the study and the number in each analysis set will be summarized by treatment panel and overall for the Randomized set.
- The number of subjects completing each treatment period will be summarized by treatment panel and overall for the Randomized set.
- The number of early withdrawals and the reasons for withdrawals will be tabulated by treatment panel and overall for the Randomized set.

6.5 Protocol Deviations

A listing of protocol deviations will be provided within Appendix 16.2 of the CSR.

6.6 Baseline Comparability

The comparability of treatment panels (Fed/Fasted) with respect to subject demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

6.6.1 Demographic Data

Standard continuous or categorical variable summaries will be presented by treatment panel and overall for the following variables based on the Safety Analysis Set.

- Sex (Male, Female)
- Age at Informed Consent (years)
- Ethnicity (Hispanic or Latino, Non-Hispanic or Latino)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple Race)
- Height at Screening (cm)
- Weight at Screening (kg)
- Body Mass Index at Screening (kg/m^2)

All demographic data will be listed.

6.7 Medical History

A listing of previous and ongoing conditions at Screening will be presented for the Safety Analysis Set. Conditions will be coded using the Medical Dictionary of Regulated Activities (MedDRA version 22.0 or higher) primary system organ class and preferred term.

6.8 Prior and Concomitant Medications

A listing of prior and concomitant medications will be provided. Prior medications are defined as all medications starting and stopping before the date of first dose of study drug. Concomitant medications are defined as medications taken on or after the date of first dose of study drug. Each concomitant medication will be assigned to the last study drug taken prior to starting the concomitant medication. Concomitant medications taken before the first dose of study drug will be assigned to 'No Treatment'. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary B3 – September 2019 version.

6.9 Exposure to Study Drug

Exposure to study medication will be tabulated by treatment panel and treatment group. All dosing information will be listed.

6.10 Statistical Analyses of Pharmacokinetic Data

6.10.1 Relative Bioavailability

The bioavailability of 4 x 50 mg dispersible tablets (Treatment B) relative to the 200-mg reference tablet (Treatment A) will be determined separately for each panel using a mixed model with log transformed PK parameters (C_{max}, AUC_{0-t}, and AUC_{0-inf}) as response variable; sequence, period, and treatment as fixed effects; and subject as random effect. The effect of dose on the relative

bioavailability of the dispersible tablets (Treatments B, C, and D) will be determined separately for each panel using a power model (Smith, 2000) of the following general form,

$$\ln(PK) = \ln(\beta_0) + \beta_1 \cdot \ln(Dose) + \varepsilon,$$

Where

PK is the pharmacokinetic parameter tested (e.g. C_{max} or AUC)

$\ln(\beta_0)$ is the y-intercept,

β_1 is the slope (a value of $\beta_1 \approx 1$ indicates linearity), and

ε is an error term

The estimate of β_1 with the 90% CIs will be reported along with the dose range for proportionality.

6.10.2 Food Effect

The effect of food on the relative bioavailability of pretomanid will be determined by comparing Panel 1 (Fed) to Panel 2 (Fasted) for each treatment using an ANOVA model with panel as the fixed effect. For informational purposes, the food effect will also be evaluated using the following ANOVA models:

1) Using data from the 4 x 50 mg dispersible tablets (Treatment B) and the 200-mg reference tablet (Treatment A) from both panels the ANOVA model will include panel, treatment, and the panel by treatment interaction term as fixed effects to determine if the food effect differs across the two treatments. A p-value equal to or smaller than 0.05 for the panel by treatment interaction term indicates that the food effect differs between the treatments. If the p-value is greater than 0.05 an ANOVA model with panel and treatment as the fixed effects will be used to determine the common food effect for Treatments A and B (Panel 1 vs Panel 2).
2) Using data from the dispersible tablets (Treatments B, C, and D) from both panels the ANOVA model will include panel, treatment, and the panel by treatment interaction term as fixed effects to determine if the food effect differs across the dispersible tablets. A p-value equal to or smaller than 0.05 for the panel by treatment interaction term indicates that the food effect differs among the dispersible tablets. If the p-value is greater than 0.05 an ANOVA model with panel and treatment as the fixed effects will be used to determine the common food effect for the dispersible tablets (Panel 1 vs Panel 2).

6.11 Safety Analyses

The safety analyses will be presented by the treatment received for the Safety Analysis Set.

6.11.1 Adverse Events

Subjects will be monitored continuously for any AEs from the time of informed consent through the end of the study. Only treatment emergent adverse events (TEAE) will be summarized. All AEs will be listed. TEAEs will be presented by treatment panel (Fed/Fasted) and overall.

A TEAE is defined as:

- Any AE that has an onset on or after the first dose of study drug through the EOS/EW follow-up visit.
- Any pre-existing AE that has worsened in severity on or after the first dose through the EOS/EW follow-up visit.

Relatedness of an AE to treatment can be classified as Not Related, Unlikely, Possible, Probable or Certain. A treatment-related AE is defined as any AE classified as possibly, probably or certainly related to the study drug. If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes.

Severity of AEs will be graded using the Division of Microbiology and Infectious Disease (DMID) Toxicity Grade November 2007 version: Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Potentially Life-Threatening). Maximum grade will be assumed for an AE with missing grade.

The following tables will be presented for AEs:

- Overall incidence and number of TEAEs, Treatment-related TEAEs, SAEs, Treatment-related SAEs, TEAEs leading to Early Withdrawal and TEAEs leading to Death.
- TEAEs by system organ class and preferred term, incidence and number of events
- Treatment-related TEAEs by system organ class and preferred term, incidence and number of events
- TEAEs by system organ class, preferred term and maximum grade, incidence
- TEAEs by system organ class, preferred term and relationship, incidence
- Listing of AEs Leading to Early Withdrawal (presented in the Table section of the appendices)
- Listing of Serious AEs (presented in the Table section of the appendices)

- Listing of Deaths (presented in the Table section of the appendices)

System organ class will be presented in descending order of overall frequency and then alphabetically. Preferred terms will be displayed in descending order of overall frequency and then alphabetically.

In counting the number of AEs reported, a continuous event (i.e. reported more than once and which did not cease), will be counted only once; non-continuous AE reported several times by the same subject will be counted as multiple events.

Where a subject reports more than one AE per system organ class and preferred term they will only be counted once for the most severe event or the most related event.

6.11.2 Laboratory Data

Descriptive statistics of the observed values and change from baseline in Period 1 to end of each treatment period (continuous data) will be presented by treatment panel and treatment group for each hematology, urinalysis and serum chemistry parameter. Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline in Period 1 to the end of each treatment period will be presented. Descriptive statistics and normal range shift tables from baseline in Period 1 to EOS/EW will also be presented overall for each treatment panel. Values will be summarized using the original units as provided by the analytical laboratory.

A listing of any clinically significant laboratory measurements recorded throughout the study will also be presented. Other laboratory data including serology, urine drug, cotinine and alcohol screening and pregnancy test data will be listed.

6.11.3 Vital Signs

Descriptive statistics for observed values and change from baseline within the relevant treatment period will be presented by treatment panel and treatment group for all scheduled measurements of the following vital signs:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration rate (breath/min)
- Body temperature (degrees Celsius)

- Body weight (kg)
- Pulse oximetry (%)

The change from baseline in Period 1 to EOS/EW will also be summarized overall. All vital sign data will be listed.

6.11.4 Electrocardiogram Data

Descriptive statistics for ECG data obtained at baseline for each treatment period will be tabulated by treatment panel and treatment group for the following variables:

- Heart Rate (bpm)
- PR Interval (ms)
- RR Interval (ms)
- QRS Complex (ms)
- QT Interval (ms)
- QTc Interval (ms) [Bazett's formula - QTcB]
- QTc Interval (ms) [Fridericia's formula - QTcF]
- Overall Interpretation

Descriptive statistics and change from baseline in Period 1 to EOS/EW will also be tabulated overall for each treatment panel.

Shift tables in relation to the overall interpretation i.e. Normal, Abnormal NCS (Not Clinically Significant), and Abnormal CS (Clinically Significant), from baseline in Period 1 to EOS/EW will be also presented overall for each treatment panel.

All ECG data, including details of any abnormalities, will be listed.

6.11.5 Physical Examination

Shift tables for the observed status of each of the body systems (Normal, Abnormal NCS, and Abnormal CS) from baseline in Period 1 to EOS/EW will be presented overall for each treatment panel.

All data, including details of clinically significant findings will be listed.

6.11.6 Taste Evaluation

Taste, Mouthfeel and Smell will be evaluated using the following categories: 1 - Like extremely, 2 - Like moderately, 3 - Neither like nor dislike, 4 - Dislike moderately and6 5 - Dislike extremely.

Taste evaluation will be summarized at each timepoint by treatment panel and treatment group. All data will be listed.

7 CHANGES TO PLANNED PROTOCOL ANALYSIS

No changes to the planned analyses have been identified.

8 REFERENCES

1. SAS Institute Inc., Cary, NC, 27513, USA
2. Phoenix™ WinNonlin® (Version 8.1, Certara L.P.)

9 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the electronic common technical document (eCTD). The eCTD section is shown in bold. The following validation methods maybe used:

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

Table Number	Table Title	Validation Method	Shell Number (if repeat)
Items in bold are not table titles but references to the section headings within eCTD.			
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14.4.6	Assessment of Dose Effect on Relative Bioavailability of Dispersible Tablets (Treatments B, C, and D) (Panel 1)		
14.4.7	Assessment of Dose Effect on Relative Bioavailability of Dispersible Tablets (Treatments B, C, and D) (Panel 2)		
14.4.8	Assessment of Food Effect Across 200 mg Treatments (A and B) on Log-Transformed PK Parameters		
14.4.9	Assessment of Food Effect Across Dispersible-Tablet Treatments (B, C, and D) on Log-Transformed PK Parameters		

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.4.1	Mean Plasma Concentration-Time Profiles of Pretomanid for Panel 1 on Linear and Semi Logarithmic Scales		
14.4.2	Mean Plasma Concentration-Time Profiles of Pretomanid for Panel 2 on Linear and Semi Logarithmic Scales		
14.4.3	Mean Plasma Concentration-Time Profiles of Pretomanid for Treatment A (Panel 1 vs Panel 2) on Linear and Semi Logarithmic Scales		
14.4.4	Mean Plasma Concentration-Time Profiles of Pretomanid for Treatment B (Panel 1 vs Panel 2) on Linear and Semi Logarithmic Scales		
14.4.5	Mean Plasma Concentration-Time Profiles of Pretomanid for Treatment C (Panel 1 vs Panel 2) on Linear and Semi Logarithmic Scales		
14.4.6	Mean Plasma Concentration-Time Profiles of Pretomanid for Treatment D (Panel 1 vs Panel 2) on Linear and Semi Logarithmic Scales		
14.4.7	All Subject Plasma Concentration-Time Profiles of Pretomanid by Treatment for Panel 1 on Linear and Semi Logarithmic Scales		
14.4.8	All Subject Plasma Concentration-Time Profiles of Pretomanid by Treatment for Panel 2 on Linear and Semi Logarithmic Scales		
14.4.9	Individual Subject Plasma Concentration-Time Profiles of Pretomanid for Panel 1 on Linear and Semi Logarithmic Scales		
14.4.10	Individual Subject Plasma Concentration-Time Profiles of Pretomanid for Panel 2 on Linear and Semi Logarithmic Scales		
14.4.11	Concentration-Time Profiles for Pretomanid with Linear Regression for Estimating the Terminal Elimination Rate		

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	**Subject Data Listings**		
16.2.1	**Discontinued Subjects**		
16.2.1.1	Subject Disposition, Early Withdrawals - All Enrolled Subjects	IP	
16.2.2	**Protocol Deviations**		
16.2.2.1	Protocol Deviations – Safety Analysis Set	IP	
16.2.3	**Subjects Excluded from the Efficacy Analyses**		
16.2.3.1	Analysis Sets	IP	
16.2.4	**Demographic Data**		
16.2.4.1	Demographic Data - Safety Analysis Set	IP	
16.2.4.2	Previous and Ongoing Medical History - Safety Analysis Set	IP	
16.2.4.3	Substance Use History - Safety Analysis Set	IP	
16.2.5	**Compliance and / or Drug Concentration Data**		
16.2.5.1	PK Sampling Information - Safety Analysis Set	IP	
16.2.5.2	Dosing Information - Safety Analysis Set	IP	
16.2.5.3	Prior and Concomitant Medications - Safety Analysis Set	IP	
16.2.6	**Individual Efficacy Response Data**		
16.2.6.1	Plasma Pretomanid Concentration Listing by Subject		
16.2.6.2	Terminal Elimination Rate of Pretomanid in Plasma for Individual Subjects (Panel 1)		
16.2.6.3	Terminal Elimination Rate of Pretomanid in Plasma for Individual Subjects (Panel 2)		
16.2.6.4	PK Output Text (WinNonlin Text File)		
16.2.6.5	SAS Output Text (Panel 1) Treatment B vs Treatment A		
16.2.6.6	SAS Output Text (Panel 2) Treatment B vs Treatment A		
16.2.6.7	SAS Output Text (Food Effect) Panel 1 vs. Panel 2		
16.2.6.8	SAS Output Text (Dose Effect) Power Model		
16.2.6.9	SAS Output Text (Panel by Treatment Interaction)		
16.2.7	**Adverse Event Listings**		
16.2.7.1	Adverse Event Data – Safety Analysis Set	IP	
16.2.8	**Individual Laboratory Measurements and Other Safety**		
16.2.8.1	Vital Signs Data - Safety Analysis Set	IP	
16.2.8.2	Physical Examination Data - Safety Analysis Set	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.8.3	Taste Evaluation Data - Safety Analysis Set	IP	
16.2.8.4	12-Lead ECG Data - Safety Analysis Set	IP	
16.2.8.5	Hematology Data - Safety Analysis Set	IP	
16.2.8.6	Serum Chemistry Data - Safety Analysis Set	IP	
16.2.8.7	Urinalysis Data - Safety Analysis Set	IP	
16.2.8.8	Urine Drug, Alcohol and Cotinine Screen Data - Safety Analysis Set	IP	
16.2.8.9	Serology Data - Safety Analysis Set	IP	
16.2.8.10	Pregnancy and FSH Test Data - Safety Analysis Set	IP	
16.2.8.11	Meal Data - Safety Analysis Set	IP	

Worldwide Clinical Trials Controlled Quality Management Document		
WORLDWIDE CLINICAL TRIALS	Sponsor:	TB Alliance
	Protocol Number:	Pa-824-CL-011

STATISTICAL ANALYSIS PLAN - TABLES, FIGURES AND LISTINGS SHELL APPROVAL

Study name:	An Open-label, Randomized, Four-period Crossover Study in Two Panels of Healthy Adult Participants to Assess the Relative Bioavailability, Food Effect, and Dose-dependence of Single-Dose Immediate-Release and Single-dose Dispersible Formulations of Pretomanid Protocol Number: Pa-824-CL-011
Statistical Analysis Plan (SAP) Version being approved:	SAP Version 1.0, dated 09-Mar-2020
Tables, Figures and Listings (TFL) Shell version being approved:	Table shells v1.0, dated 09-Mar-2020 Listing shells v1.0, dated 09-Mar-2020

The above SAP / TFL Shell has been reviewed and approved by Worldwide:

Name of Author:	**Aimie Nunn**
Position:	**Senior Statistician**
Signature:	DocuSigned by: Aimie Nunn Signer Name: Aimie Nunn Signing Reason: I approve this document Signing Time: 09-Mar-2020 | 14:35:07 GMT 339619CFC74243318859B713A386896B
Date:	
Author:	**Kathryn Roupe Ph.D.**
Position:	**Principal Research Scientist, Pharmacokinetics**
Signature:	DocuSigned by: Kathryn Roupe Signer Name: Kathryn Roupe Signing Reason: I am the author of this document Signing Time: 09-Mar-2020 | 14:41:03 GMT A2103069EADE42BA87CC9685DDF4E5A1
Date:	

Worldwide Clinical Trials Controlled Quality Management Document		
WORLDWIDE CLINICAL TRIALS	Sponsor:	TB Alliance
	Protocol Number:	Pa-824-CL-011

STATISTICAL ANALYSIS PLAN - TABLES, FIGURES AND LISTINGS SHELL APPROVAL

The above SAP / TFL Shell has been reviewed and approved by Worldwide:

Name of Reviewer: **Michael Jones**

Position: **Statistician**

Signature:

DocuSigned by:
Michael Jones
Signer Name: Michael Jones
Signing Reason: I have reviewed this document
Signing Time: 09-Mar-2020 | 14:41:55 GMT
73AFDF654F3A4785974EFAECAE63CAA8

Date:

The above SAP / TFL Shell has been reviewed and approved by the Sponsor:

Name of Sponsor Clinical Lead: **Jerry Nedelman**

Position: **Senior Director Pharmacometrics**

Signature:

DocuSigned by:
Jerry Nedelman
Signer Name: Jerry Nedelman
Signing Reason: I approve this document
Signing Time: 09-Mar-2020 | 09:05:29 PDT
7839E5A76523498AB928E27ED5F738EA

Date:

Worldwide Clinical Trials Controlled Quality Management Document		
WORLDWIDE CLINICAL TRIALS	Sponsor:	TB Alliance
	Protocol Number:	Pa-824-CL-011
STATISTICAL ANALYSIS PLAN SUPPLEMENT		

Statistical Analysis Plan Supplement

An Open-label, Randomized, Four-period Crossover Study in Two Panels of Healthy Adult Participants to Assess the Relative Bioavailability, Food Effect, and Dose-dependence of Single-Dose Immediate-Release and Single-dose Dispersible Formulations of Pretomanid

Protocol Number: *Pa-824-CL-011*

Protocol Version: *1.0, dated 06-Dec-2019*

SAP Version: *1.0, dated 09-March-2020*

Supplement Version: *1.0*

Supplement Issue Date: *07-Jul-2020*

Previous Supplements

Not Applicable

Worldwide Clinical Trials Controlled Quality Management Document		
WORLDWIDE CLINICAL TRIALS	Sponsor:	TB Alliance
	Protocol Number:	Pa-824-CL-011
STATISTICAL ANALYSIS PLAN SUPPLEMENT		

1. BACKGROUND

This document details cosmetic / typographical changes only, which have no bearing or impact on the analysis or interpretation of results for TB Alliance, protocol *"Pa-824-CL-011"* study previously described in Version 1.0 of the Statistical Analysis Plan dated 09-March-2020. These amendments were made post database lock; however, the study was open label.

2. CHANGES TO EXISTING SAP

No changes to existing text.

3. ADDITIONS TO EXISTING SAP

No additions to existing text.

4. CHANGES TO TABLES, FIGURES AND LISTINGS (TFL) SHELL TABLE OF CONTENT (TOC) WITHIN SAP

For the following Listing, the Analysis Set was amended in the final output:

Described in the SAP

16.2.1.1 Subject Disposition, Early Withdrawals - All Enrolled Subjects

Presented in the final Listing

16.2.1.1 Subject Disposition, Early Withdrawals – Randomized Set

New TOC attached: ☐ yes ☒ no

5. CHANGES TO TFL SHELL

No TFL changes.

Worldwide Clinical Trials Controlled Quality Management Document		
WORLDWIDE CLINICAL TRIALS	Sponsor:	TB Alliance
	Protocol Number:	Pa-824-CL-011
STATISTICAL ANALYSIS PLAN SUPPLEMENT		

Approval for Implementation of

Statistical Analysis Plan Supplement

The changes detailed above are purely cosmetic and have no impact on the planned analysis or interpretation of results:

Name of Author: **Aimie Nunn**

Position: **Senior Statistician**

Signature: DocuSigned by: Aimie Nunn

Date: Signer Name: Aimie Nunn
Signing Reason: I am the author of this document
Signing Time: 07-Jul-2020 | 16:38:19 BST
339619CFC74243318859B713A386896B

Name of Reviewer: **Michael Jones**

Position: **Statistician**

Signature: DocuSigned by: Michael Jones

Date: Signer Name: Michael Jones
Signing Reason: I have reviewed this document
Signing Time: 08-Jul-2020 | 03:30:35 CDT
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