CLINICAL STUDY PROTOCOL

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

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PROTOCOL APPROVAL PAGE

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Protocol Number: Pa-824-CL-011

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11 DEC 2019

PROTOCOL SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company: TB Alliance</td></tr>
<tr><td colspan="2">Name of test product: Pretomanid</td></tr>
<tr><td colspan="2">Name of active ingredient: Pretomanid</td></tr>
<tr><td colspan="2">Title of study: 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</td></tr>
<tr><td colspan="2">Principal Investigator: Cynthia A. Zamora, MD</td></tr>
<tr><td colspan="2">Study Center:
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San Antonio, Texas 78217</td></tr>
<tr><td>Study period (maximum duration, from screening to study exit): 54 days</td><td>Phase of development: 1</td></tr>
<tr><td>Duration of treatment:
26 days with a follow-up visit 7 days following the last PK sample in the last treatment session (or after drop-out). Four single-dose treatments will be administered to each subject with a 7-day washout period between each dose.</td><td>Number of sites enrolling subjects: 1</td></tr>
<tr><td colspan="2">Number of evaluable subjects (planned): 48 (2 panels of 24 participants each).</td></tr>
<tr><td colspan="2">Diagnosis and main criteria for inclusion:
Volunteers will be healthy adult males or females, 19 to 50 years of age (inclusive).</td></tr>
<tr><td colspan="2">Objectives:
<u>Primary Objective:</u>
• 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.
<u>Secondary Objectives:</u>
• 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.</td></tr>
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Study design overview:

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.

Investigational products, dosages and mode of administration:

1) Treatment A (reference) = 200 mg given as a single 200 mg tablet (using the immediate release formulation), orally administered.
2) Treatment B (test) = 200 mg given as four 50-mg tablets (using the dispersible pediatric formulation), orally administered.
3) Treatment C (test) = single 50-mg dispersible tablet, orally administered.
4) Treatment D (test) = single 10-mg dispersible tablet, orally administered.

Subjects in Panel 1 will be administered each treatment above after a 10-hour overnight fast and a high-fat, high-calorie breakfast. Subjects in Panel 2 will be administered each treatment above after a 10-hour overnight fast.

Criteria for evaluation:

Pharmacokinetics:

Full pharmacokinetic 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 pharmacokinetic measures include T_{max}, C_{max}, AUC_{0-t}, and $AUC_{0-inf.}$ Secondary pharmacokinetic measures include the ratio of AUC_{0-t} to AUC_{0-inf}, $T_{1/2}$, K_{el}, Cl/F and Vd/F.

Statistical summaries for a given period will include data from all subjects for whom it was a completed period, even those who do not complete all four periods. The primary mixed-model analyses for relative bioavailability, dose, and food will use all the data from all completed periods.

Descriptive statistics will be used to summarize pretomanid plasma concentrations at each sampling time point and for derived plasma PK parameters, as applicable. Statistics include sample size (n), mean, SD, percentage coefficient of variation (% CV), geometric mean, median, minimum, and maximum.

All data will be listed, even if not used for statistical summaries or model-based analyses. But data that do not come from completed periods will be characterized in the listing as to their deficiency.

For each participant, pretomanid plasma concentration-time data will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined

individual plasma concentration-time profiles will be produced. Additionally, pharmacokinetic parameters may be explored graphically.

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

The effect of dose on the relative bioavailability of the dispersible tablet will be determined separately for each panel using the same model as above.

The effect of food on the relative bioavailability of pretomanid will be determined comparing, across panels, each formulation and dose taken after eating breakfast versus the same formulation and dose taken in fasted conditions using a mixed model with the log transformed PK parameter as response variable; panel, sequence, period, treatment, and panel-by-treatment interaction as fixed effects; and participant as random effect.

The T_{max} of pretomanid for each of the formulations will be descriptively compared.

Other statistical models and/or population pharmacokinetic modelling may also be used for further data interpretation.

Safety:

The Investigator will evaluate safety using the following assessments: 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. In addition, vital signs will be investigated prior to each dose and daily, as well as 7 days after the last PK sample. ECGs will be obtained prior to each dose and 7 days after the last PK sample. Clinical laboratory tests will be investigated prior to each dose and 96 hours post-dosing as well as 7 days after the last PK sample. Safety follow-up is planned 7 days following the last PK sample in the last treatment session (or after drop-out).

Efficacy: No efficacy evaluations will be performed in this study.

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LIST OF ABBREVIATIONS

ADL	activity of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the (plasma concentration vs. time) curve
AUC_{last}	area under the curve from time 0 hours to last quantifiable concentration
$AUC_{0\text{-}inf}$	area under the curve from time 0 hours to infinity
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
bpm	beats per minute
Ca	calcium
CFR	Code of Federal Regulations
CI	confidence interval
Cl^-	chloride
C_{last}	last quantifiable drug concentration
Cl/F	apparent clearance
CLIA	Clinical Laboratory Improvement Amendments
cm	centimeter(s)
C_{max}	maximum concentration
CNS	central nervous system
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DEA	Drug Enforcement Administration
dL	deciliter
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
ER	extended-release
FDA	Food and Drug Administration
fl	fluid
FSH	follicle-stimulating hormone
g	gram(s)
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HCl	hydrochloride

ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug
IP	Investigational Product
IR	immediate-release
IRB	institutional review board
ISF	Investigator Site File
IUD	intrauterine device
K^+	potassium
K_{el}	the elimination rate constant
kg	kilogram(s)
L	liter(s)
lbs	pounds
LDH	lactate dehydrogenase
LOQ	limit of quantitation
m	meter(s)
MAOI	monoamine oxidase inhibitor
max.	maximum
mg	milligram(s)
min.	minute(s)
mIU	milli international units
mL	milliliter(s)
mmHg	millimeter of mercury
msec	millisecond
n or N	number of occurrences
Na^+	sodium
ng	nanogram(s)
OTC	Over-the-counter
oz	ounce(s)
RBC	red blood cell
RLD	reference listed drug
rpm	revolutions per minute
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
$T_{½}$ or $t_{½}$	terminal elimination half-life
T_{lag}	time prior to the first measurable (non-zero) concentration
T_{last}	time of the last measurable concentration
T_{max}	time to reach C_{max}
Vd/F	apparent volume of distribution

UDS	urine drug screen
WBC	white blood cells
WCT	Worldwide Clinical Trials Early Phase Services/Bioanalytical Sciences, LLC
β-hCG	beta-human chorionic gonadotropin
λ_z or Lambda-z	apparent elimination rate constant in terminal phase
°C	degrees Celsius/Centigrade

1 INTRODUCTION

TB Alliance has developed two investigational formulations (10- and 50- mg dispersible tablets) of pretomanid (PA-824) that are intended for pediatric use. In the present study, the pharmacokinetics (PK) and safety of the dispersible formulations will be compared to the approved (reference) pretomanid (PA-824) 200 mg tablet. This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

Pretomanid is indicated in combination with bedaquiline and linezolid for the treatment of extensively resistant pulmonary tuberculosis (XDR-TB) and of multidrug-resistant pulmonary (MDR) TB that is non-responsive to treatment or with demonstrated treatment intolerance. The purpose of the present study is to investigate pretomanid formulations that could be used for the treatment of XDR-TB and non-responsive or treatment-intolerant MDR-TB in children, as part of a combination regimen that will also include bedaquiline and linezolid. The safety and pharmacokinetic information below is excerpted from the Investigator's Brochure (IB) for Pretomanid (PA-824).[1]

1.1 Clinical Studies[1]

The clinical program of pretomanid has included Phase 1 studies in healthy volunteers to evaluate the safety, tolerability, and PK of this novel agent in humans, as well as Phase 2 trials to explore its mycobactericidal activity, dose response, PK, and safety in subjects with newly diagnosed pulmonary TB. At the time of the IB data cut-off data (26 May 2019), pretomanid, either alone or as part of a combination regimen, has been used in at least 26 clinical trials sponsored by either TB Alliance or another entity in more than 1,664 subjects. Twenty-one of the trials are considered as the core of the pretomanid developmental program. Safety data for pretomanid summarized below are based on 1,153 subjects from 19 trials, including 208 subjects with either XDR-TB or MDR-TB, 656 subjects with drug susceptible (DS)-TB, and 289 healthy volunteers.

In these trials, pretomanid was either administered alone or as part of a combination regimen (see Appendix 2 in the IB[1]). Adverse events (AEs) were identified from the pooled safety database based upon a systematic and well-documented approach. The profile for common AEs varied across the pooling groups, most likely due to variations in subject population, the types of drugs used in the treatment regimens, and the duration of exposure. In the Phase 1 pool, in which 174 subjects were exposed to a single dose of pretomanid ranging from 50 to 1500 mg, and 115 subjects were exposed to repeated daily doses of pretomanid ranging from 200 mg to 1000 mg for up to 14 days, at least 1 AE was reported in 64.4% of pretomanid-treated subjects (the all-pretomanid group) and in 40.0% of control subjects. The incidence of any AE was lower in the single-dose pretomanid ≤200 mg group than in the other pretomanid groups (33.3% versus a range of 66.7% to 70.3%). The most frequently (≥10% of

subjects) reported AEs in the all-pretomanid group were headache (31.5%), nausea (11.8%), decreased hemoglobin (10.7%), and contact dermatitis (11.4%). The only AE in the control group reported in at least 10% of subjects was headache, with an incidence lower than that in the all-pretomanid group (22.9% versus 31.5%). Headache was more common in the multiple-dose pretomanid >200 mg group than in the other pretomanid groups (45.6% versus a range of 25.9% to 29.0%). Nausea occurred more frequently in the single- and multiple-dose pretomanid >200 mg groups (13.8% and 14.0%, respectively) than in the single-dose pretomanid ≤200 mg and multiple-dose 200 mg groups (5.6% and 8.6%, respectively). Decreased hemoglobin and contact dermatitis were observed primarily in the single-dose pretomanid >200 mg group (22.5% versus 0% for other pretomanid groups for hemoglobin decreased; 23.2% versus a range of 0% to 1.8% for dermatitis contact. The decrease in hemoglobin); occurred primarily in the thorough QT study which involved multiple blood draws and ECG pad applications.

Treatment-related AEs identified from the pooled safety database of reported AEs in the Phase 1 studies where placebo arm was available, and Phase 2 and 3 clinical studies where a standard of care arm was available included nausea, vomiting, rash, and increased transaminases. Increased transaminases were not seen in Phase 1 studies but were reported in studies that enrolled patients with MDR-TB or XDR-TB who had multiple comorbidities and received pretomanid in combination with other anti-tuberculosis drugs.

1.2 Pharmacokinetics[1]

Important drivers of PK variability are dosing with or without food, and co-administration of medications that induce CYP3A4.

Bioavailability in the fasted state was about half that in the fed state, when pretomanid was administered at the clinical dose of 200 mg.

In the presence of rifampicin and efavirenz, pretomanid area under the curve (AUC) was reduced 66% and 35%, respectively. Such strong and moderate CYP3A4 inducers should be avoided with pretomanid. No clinically significant differences in the pharmacokinetics of pretomanid were observed based on sex, body weight, race (black, Caucasian, or other), pulmonary TB status, or human immunodeficiency status (HIV) status. The effect of renal or hepatic impairment on the pharmacokinetics of pretomanid is presently unknown but is being investigated in two ongoing studies.

1.3 Study Rationale

MDR- and XDR-TB have become more and more widespread. Treatment requires complex, prolonged regimens with significant toxicity and relatively low cure rates. In August 2019, FDA approved the use of pretomanid, in combination with bedaquiline and linezolid (BPaL regimen), for the treatment of XDR-TB and selected forms of

MDR-TB. This all-oral, 6-month treatment regimen, was associated with cure rates of approximately 90% and manageable toxicity. MDR- and XDR-TRB are less common in children, it is expected that their incidence in this population will increase due to increasing transmission of drug-resistant MTb strains. Therefore, there is an important, unmet medical need to investigate treatment options for drug-resistant forms of TB in pediatric patients. Our future goal is to investigate the BPaL regimen in children with MDR- and XDR-TB. The present trial is designed to investigate 2 pretomanid formulations intended for pediatric use.

Pretomanid is provided for adults as an immediate release tablet with 200 mg active substance. The same product is foreseen for adolescents 12 years and older. For patients younger than 12 years, dispersible scored tablets containing 10 and 50 mg pretomanid are currently being developed, which would be used to adjust doses based on body weight.

An extrapolation approach is intended for the pediatric clinical development program: This will be based on the identification of doses in children yielding exposure to pretomanid that corresponds to the exposure in adult patients where efficacy has been demonstrated.

This study will evaluate the relative bioavailability of the dispersible tablet compared to that of the immediate release tablet used for dosing of adolescents and adults. In addition, a potential food effect will be evaluated. This study will be conducted in healthy adult volunteers.

2 OBJECTIVES

Primary Objective:

- 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.

Secondary Objectives:

- 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 STUDY DESIGN SUMMARY

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. Figure 1 shows the trial schematic.

Figure 1 Trial Schematic

Session I **(Days 1-5)**	**Days 6, 7**	**Session II** **(Days 8-12)**	**Days 13, 14**
Panel 1: Treatment A, B, C or D (single dose) with breakfast or Panel 2: Treatment A, B, C or D after a 10-hour overnight fast	2-day break	Panel 1: Treatment A, B, C or D (single dose) with breakfast or Panel 2: Treatment A, B, C or D after a 10-hour overnight fast	2-day break
Session III **(Days 15-19)**	**Days 20, 21**	**Session IV** **(Days 22-26)**	**Follow-up Visit** **(Day 33)**
Panel 1: Treatment A, B, C or D (single dose) with breakfast or Panel 2: Treatment A, B, C or D after a 10-hour overnight fast	2-day break	Panel 1: Treatment A, B, C or D (single dose) with breakfast or Panel 2: Treatment A, B, C or D after a 10-hour overnight fast	7 days after last PK sample in Session IV

The screening period will begin within 21 days of the first participant being dosed. Subjects will be assigned numbers in an ascending order, based on successful completion of the screening process.

Subjects will receive a single dose of each treatment listed in Table 1 in randomized fashion during the four treatment periods.

Table 1 Identity of Investigational Products

Reference Product: Treatment A	Pretomanid (PA-824)
	Dose = 1 x 200-mg tablet (using the immediate release formulation), orally administered
	TB Alliance
Test Product: Treatment B:	Pretomanid (PA-824)
	Dose = 4 x 50-mg dispersible tablets (200 mg total), orally administered (as dispersion in water)
	TB Alliance
Test Product: Treatment C:	Pretomanid (PA-824)
	Dose = 1 x 50-mg dispersible tablet, orally administered (as dispersion in water)
	TB Alliance
Test Product: Treatment D:	Pretomanid (PA-824)
	Dose = 1 x 10-mg dispersible tablet, orally administered (as dispersion in water)
	TB Alliance

Each study treatment administration will be separated by a washout period of 7 days. An outpatient safety follow-up visit is planned approximately 7 days following the last pharmacokinetic sample in the last treatment period (or after drop-out).

During each study period, 120 mL blood samples will be obtained before study drug administration and at selected times through 96 hours after study drug administration. A total of 60 pharmacokinetic blood samples will be collected from each subject, 15 samples in each study period. Plasma pharmacokinetic samples will be analyzed for pretomanid using a validated analytical method. Appropriate pharmacokinetic parameters will be calculated for each formulation using non-compartmental methods.

Food and water consumption will follow the guidelines in Section 5.4. Subjects who withdraw from the study will not be replaced.

4 SUBJECT SELECTION

4.1 Inclusion Criteria

All volunteers must satisfy the following criteria to be considered for study participation:

1. Voluntarily consents to participate in this study and provides written informed consent before the start of any study-specific procedures.
2. Male or female. Females must not be pregnant or breastfeeding.
3. Willing and able to comply with the contraception requirements (see Section 4.4).
4. Between 19 and 50 years of age (inclusive) at the time of screening.

5. Body mass index (BMI) between 18.50 and 32 kg/m^2 (inclusive) and weighs a minimum of 50 kg.
6. Willing and able to remain in the study unit for the entire confinement period and return for the outpatient follow-up visit.
7. Willing and able to consume the entire high-calorie, high-fat breakfast meal in the timeframe required during the designated study period.
8. Willing and able to comply with the protocol and the assessments therein, including all restrictions.

4.2 Exclusion Criteria

Volunteers will be excluded from study participation for any of the following:

1. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease or any other condition that, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.
2. A clinically significant abnormal finding on the physical examination, medical history, electrocardiogram (ECG), or clinical laboratory results.
3. Vital signs at screening (measured sitting after a minimum 3 minutes rest) as follows: blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg or a heart rate lower than 40 bpm or higher than 99 bpm. Out-of-range vital signs may be repeated once.
4. History or presence of allergic or adverse response to pretomanid or related drugs.
5. On a significantly abnormal diet during the 4 weeks preceding the first dose of study medication.
6. Participation in another clinical trial (randomized subjects only) within 30 days before the first dose of study medication.
7. Use of any over-the-counter (OTC) medication (including nutritional or dietary supplements, herbal preparations, or vitamins) within 7 days before the first dose of study medication until the end of study visit without evaluation and approval by the Investigator. Up to 3 grams per day of acetaminophen is allowed at the discretion of the Investigator prior to dosing.
8. Use of any prescription medication, except hormonal contraceptive or hormonal replacement therapy, from 14 days before the first dose of study medication until the end-of-study visit without evaluation and approval by the Investigator.
9. Use of any drugs or substances known to lower the seizure threshold.

10. Use of any drugs or treatment with any known drugs that are moderate or strong inducers or inhibitors of cytochrome P450 (CYP) enzymes (e.g., barbiturates, phenothiazines, cimetidine, carbamazepine) and/or P-gp, including St. John's Wort, within 30 days before the first dose of study medication, and that, in the Investigator's judgment, may impact subject safety or the validity of the study results.
11. Female with a positive pregnancy test result.
12. Positive urine screen for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, opiates) or cotinine.
13. Positive test for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) at screening or has been previously treated for hepatitis B, hepatitis C, or HIV infection.
14. Hemoglobin <10.0 g/dL.
15. ALT or AST >2.0 x the upper limit of normal (ULN).
16. Hyperbilirubinemia >1.5 x ULN.
17. Surgery within the past 90 days prior to dosing as determined by the Investigator to be clinically relevant.
18. History or presence of alcoholism or drug abuse within the past 2 years as determined by the Investigator to be clinically relevant.
19. Any clinically significant electrocardiogram abnormality at Screening (as deemed by decision of the Investigator and the Study Sponsor's Medical Monitor).

    Note: The following may be considered not clinically significant without consulting the Sponsor's Medical Monitor:

    a. Mild first-degree A-V block (P-R interval <0.23 sec)
    b. Right or left axis deviation
    c. Incomplete right bundle branch block
    d. Isolated left anterior fascicular block (left anterior hemiblock) in younger athletic participants.
20. QTcF interval >450 msec for males or >470 msec for females at screening, Day -1, or Day 1 (pre-dose), or history of prolonged QT syndrome.
21. Family history of Long-QT Syndrome or sudden death without a preceding diagnosis of a condition that could be causative of sudden death (such as known coronary artery disease, congestive heart failure or terminal cancer).

4.3 Activity Restrictions

1. Subject must not donate blood from 56 days or plasma from 7 days prior to the first dose of study medication until after follow-up phone call. It is recommended that blood/plasma donations not be made for at least 30 days after discharge from the clinic.
2. Subject must not use tobacco- or nicotine-containing products (including smoking cessation products) from 6 months prior to the first dose of study medication until after the follow-up phone call.
3. Subject must not consume alcohol from 72 hours prior to the first dose of study medication until after discharge from the clinic.
4. Subject must not consume beverages or foods that contain grapefruit or Mandarin oranges from 10 days before the first dose of study medication, or poppy seeds, broccoli, Brussels sprouts, pomegranate, star fruit, or caffeine/xanthine from 48 hours before the first dose of study medication, until after discharge from the clinic. Participants will be instructed not to consume any of the above products; however, allowance for an isolated single incidental consumption may be evaluated and approved by the study Investigator based on the potential for interaction with the study drug.
5. Subject must not engage in strenuous exercise from 48 hours prior to the first dose of study medication until after discharge from the clinic.
6. Male subjects must not donate sperm throughout treatment and for at least 12 weeks after the last dose of trial medication or discontinuation from trial medication in case of premature discontinuation.

4.4 Contraception Requirements

Female subjects must plan not to conceive throughout treatment and for at least 1 week after the last dose of trial medication or discontinuation from trial medication in case of premature discontinuation.

Male subjects must plan not to conceive or donate sperm throughout treatment and for at least 12 weeks after the last dose of trial medication or discontinuation from trial medication in case of premature discontinuation.

Subjects must be of non-childbearing potential, defined as:

- Male or female subjects - is not heterosexually active or practices sexual abstinence.
- Female subjects or male subjects with a female sexual partner- bilateral oophorectomy, bilateral tubal ligation and/or hysterectomy.

- Female subjects-postmenopausal with amenorrhea for at least 1 year prior to the first dose with serum follicle-stimulating hormone (FSH) levels consistent with postmenopausal status at screening.
- Male subject or female participant male sexual partner – vasectomized or has had bilateral orchidectomy minimally three months prior to screening.

Or

Be willing to use an effective method of birth control, defined as:

- Male subjects with a female sexual partner- double barrier method or hormone-based contraceptives or an intra-uterine device for the female partner.
- Female subjects- double barrier method which can include a male condom, diaphragm, cervical cap, or female condom; or
- Female subjects- barrier method combined with hormone-based contraceptives or an intra-uterine device.

Note: Hormone-based contraception alone may not be reliable when taking the study drugs; therefore, hormone-based contraceptives alone cannot be used by female subjects to prevent pregnancy.

4.5 Screening

The informed consent documents will be discussed with each potential participant, and each individual will sign an informed consent document for the study before any study-specific procedures being performed.

Each potential study participant will have the following assessments by the Investigator or designee within 21 days before study start:

- Medical history and demographic data, including sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2), and smoking habits.
- Physical examination
- Vital signs
- ECG
- Clinical laboratory tests
- Serology tests
- Urine test for drugs of abuse, alcohol, and cotinine
- Serum pregnancy test (all female subjects)
- FSH test (Post-menopausal females)

Only medically healthy subjects with clinically acceptable laboratory profiles and ECGs will be enrolled in the study.

5 STUDY PROCEDURES

5.1 Subject Assignment

Two panels of healthy male and female subjects (24 participants 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.

Subjects will be randomized to a panel, and the two panels will be investigated concurrently. Additionally, subjects in each panel will be randomized according to the same 4-sequence, 4-period Williams design in which each participant will receive four single-dose treatments.

The maximum duration of the study from screening to study exit will be approximately 54 days.

This is an open-label study without treatment blinding.

5.2 Check-In Procedures

At clinic check-in (Day -1), all subjects will be evaluated to confirm they continue to meet all the inclusion criteria (Section 4.1) and none of the exclusion criteria (Section 4.2).

A urine sample will be collected from all subjects at study check-in to screen for drugs of abuse, cotinine, and alcohol. If at any time an alcohol, drug, or cotinine test is positive, the subject will be discontinued from study participation.

Subjects of childbearing potential will be asked to confirm that they still adhere to the contraceptive criteria (Section 4.4). Each subject's response will be documented.

A blood sample will be collected from all female subjects for a serum pregnancy test. This test must be negative for the subject to continue study participation.

An abbreviated physical examination will be performed, including measurement of weight.

Blood and urine will be collected for clinical laboratory tests (hematology, chemistry and urinalysis).

Vital signs (blood pressure, pulse, temperature, respiration rate, and pulse oximetry) will be measured and a single 12-lead ECG performed.

Any changes to medical history and/or concomitant medication will be recorded.

5.3 Confinement

Subjects will be admitted to the research center at an appropriate time the day before the first study drug administration in order to ensure a minimum 10-hour overnight fast.

Subjects will be confined in the facility from check-in (Day -1) until completion of the 4-day post-dose procedures in Period 4 (Study Day 26) and return for a follow-up safety visit on Day 33.

5.4 Fasting/Meals/Beverages

5.4.1 Fasting/Meals

Panels 1 & 2

An optional meal or snack will be served the evening of each check-in. All subjects will fast for at least 4 hours after each dose. Standard meals will be provided at approximately 4 and 10 hours after each drug administration and at appropriate times thereafter. Meal/snack menus will be the same for all study periods.

Subject must not consume beverages and foods containing alcohol, grapefruit, poppy seeds, broccoli, Brussels sprouts, pomegranate, star fruit, char-grilled meat, or caffeine/xanthine from 48 hours before the first dose of study medication until the end-of-study visit. Subjects will be instructed not to consume any of the above products; however, allowance for an isolated single incidental consumption may be evaluated and approved by the study investigator based on the potential for interaction with the study drug.

Panel 1 (fed)

Subjects in Panel 1 will be required to fast for at least 10 hours before consuming a required FDA standard high-fat, high-calorie breakfast. Subjects will receive the breakfast to begin 30 minutes before scheduled administration of the dose and to end (last bite taken) within 5 minutes before dosing. The subjects will fast for 4 hours thereafter. The following high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 1000 calories) breakfast will be ingested 30 minutes before administration of the drug:

2 eggs fried in butter
2 strips of bacon
2 slices of toast with butter
4 ounces of hash brown potatoes
8 ounces of whole milk

This meal contains approximately 150 protein calories, 250 carbohydrate calories, and 500-600 fat calories. An equivalent meal may be substituted with documentation of the menu and caloric contents. The amount consumed by subjects will be recorded.

Panel 2 (fasted)

Subjects in Panel 2 will be required to fast for at least 10 hours before dosing.

5.4.2 Beverages

Except for the room temperature water provided with the study treatment, no water may be consumed for 1 hour before each dose through 1 hour after each dose. At other times, subjects will be encouraged to drink water ad libitum.

5.5 Drug Administration

Subjects will be administered Treatment A (1 x 200-mg tablet using the immediate release formulation) with 240 mL of ambient room temperature water. Subjects must swallow the tablet intact; it should NOT be crushed or chewed.

Subjects will be administered Treatment B (4 x 50-mg dispersible tablets) as follows: clinic staff will disperse each tablet in 10 mL of ambient room temperature water, which subjects will swallow. Following each 10 mL dose, clinic staff will then rinse the same container with an additional 10 mL of ambient room temperature which the subjects will swallow. Subjects will then rinse their mouths and swallow an additional 25 mL of ambient room temperature water.

Subjects will be administered Treatment C (1 x 50-mg dispersible tablet) as follows: clinic staff will disperse the tablet in 10 mL of ambient room temperature water, which subjects will swallow. Clinic staff will then rinse the same container with an additional 10 mL of ambient room temperature water, which the subjects will swallow. Subjects will then rinse their mouths and swallow an additional 25 mL of ambient room temperature water.

Subjects will be administered Treatment D (1 x 10-mg dispersible tablet) as follows: clinic staff will disperse the tablet in 10 mL of ambient room temperature water, which subjects will swallow. Clinic staff will then rinse the same container with an additional 10 mL of ambient room temperature water, which the subjects will swallow. Subjects will then rinse their mouths and swallow an additional 25 mL of ambient room temperature water.

Additional details will be provided in a separate manual.

For all treatments, a mouth check will be performed immediately after each dose to ensure that the study drug was appropriately swallowed. A hand check will also be performed after Treatment A.

The subjects will remain seated, except as otherwise required for study procedures or personal needs, for the first 4 hours after dosing. Should the need to move about occur during the first 4 hours after each dose, subjects may be escorted to such procedures or activities by research personnel as deemed medically necessary. Subjects will not be

allowed to lie down, except as directed by clinical staff secondary to AEs, for the first 4 hours after dosing.

5.6 Blood Sampling, Processing and Shipment

Blood samples for analysis of pretomanid concentrations will be drawn just before each drug administration (pre-dose), and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours after each dose. A total of 120 mL (60 x 2.0 mL samples) will be collected from each subject for pharmacokinetic analysis. Blood samples will be collected as detailed in Appendix I, Pharmacokinetic Sample Collection, Processing, and Shipment Instructions.

- Blood samples collected up to and including 24 hours post-dose within ± 2 minutes of scheduled time will not be considered deviations.
- Blood samples collected after 24 hours post-dose within ± 5 minutes of scheduled time will not be considered deviations.

Table 2 Acceptable Pharmacokinetic Sampling Time Windows

Investigation and examination	Allowable Time Window	
	Post-dose	
	≤24 hours	>24 hours
Plasma sample collection for pharmacokinetic assessment	± 2 minutes	± 5 minutes

In addition, approximately 87.5 mL of blood in total will be collected during the study for the clinical laboratory evaluations at the timepoints shown in Table 5. The total volume of blood collected from each subject in each treatment session will not exceed approximately 145 mL.

Additional blood may be collected, if necessary, for repeat laboratory evaluations or AE follow up.

5.7 End-of-Study Procedures

Subjects will return to the clinic for a follow-up safety visit approximately 7 days after their final dose of study medication. During this visit, the following procedures will be conducted:

- Blood and urine will be collected for clinical laboratory tests (hematology, chemistry and urinalysis)
- Vital signs (blood pressure, pulse, temperature, respiration rate, and pulse oximetry)
- Single 12-lead ECG

- Physical examination
- Drug, cotinine, and alcohol testing
- Urine pregnancy test (all female subjects)
- Any updates to AEs and/or concomitant medication

When possible, end-of-study procedures will be performed in the event of a subject's early termination from the study.

5.8 Safety Monitoring and Procedures

5.8.1 Safety – Adverse Events

Subjects will be instructed to inform the study physician and/or research personnel of any AEs that occur at any time during the study. Subjects will be monitored for AEs from the signing of the informed consent through the follow-up visit.

Refer to Section 6 for details regarding AE reporting.

5.8.2 Safety – Clinical Laboratory Evaluations

- Clinical laboratory tests (hematology, serum chemistry, and urinalysis) will be performed at the timepoints shown in the Events Schedule (Table 5).
  - Hematology: hemoglobin, hematocrit, total and differential leukocyte count, red blood cell count, and platelet count.
  - Serum chemistry: albumin, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate transaminase, alanine transaminase, sodium, potassium, chloride, lactate dehydrogenase, calcium, uric acid, glucose, gamma-glutamyl transferase, and magnesium.
  - Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocyte esterase and urobilinogen. If protein, occult blood, nitrite or leukocyte esterase values are out of range, a microscopic examination will be performed.
- Serology - Blood will be tested for hepatitis B surface antigen, hepatitis C antibody, and HIV at screening.
- Urine Drug, Cotinine, and Alcohol Screens - Urine samples will be tested for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opiates) cotinine, and alcohol at screening and check-in.
- For all female subjects: a serum pregnancy test at screening and check-in, and a urine pregnancy test at the follow-up visit.
- Follicle-stimulating hormone (post-menopausal females) at screening.

A Clinical Laboratory Improvement Amendments (CLIA) certified laboratory will perform all clinical laboratory tests for this study.

5.8.3 Safety – Vital Signs

Vital signs (blood pressure, pulse rate, respiration rate, temperature, and pulse oximetry) will be measured at the timepoints shown in the Events Schedule (Table 5).

Both blood pressure and heart rate (pulse) should be captured simultaneously. Blood pressure and heart rate should be measured after participants are in a seated position for at least 2 minutes and then again after standing for 1 minute, except when they are supine or semi-reclined because of study procedures and/or adverse events, or as deemed necessary by the Investigator.

Pre-dose vital signs will be assessed by the Principal Investigator or designee (e.g., a medically qualified Sub-Investigator) before each study drug administration. The Principal Investigator or designee will verify the eligibility of each subject with out-of-range vital signs and document approval before dosing.

Additional vital signs measurements may be performed as deemed medically necessary by research personnel. All vital signs measurements will be taken after the subject has completed a minimum 3-minute sit.

5.8.4 Safety – Physical Examinations

A full physical examination will be performed at screening. An abbreviated physical examination will be performed at check-in (Day -1) and at end-of-study/early termination. Height will only be collected at screening.

5.8.5 Safety – Electrocardiograms

A single 12-lead ECG will be performed after the subject has been in supine position for a minimum of 5 minutes at screening and on Study Days 1, 8, 15 and 22. They must be performed within 2 hours prior to dosing and completed 20 minutes prior to pre-dose blood draw. ECGs will be printed and reviewed on-site by the Principal Investigator or designee.

5.8.6 Other Safety Measures

Medical emergency personnel trained in advanced cardiac life support will be on site to monitor subjects during the confinement period in the research center. Emergency medical equipment including but not limited to intubation equipment and pulse oximetry shall be maintained on site to administer appropriate medical care should it be required.

Procedures will be completed as specified in this protocol unless contraindicated due to a reported AE.

6 ADVERSE EVENTS

The Investigator or a suitably medically qualified designee are responsible for eliciting adverse events by observing and questioning the subject and recording all adverse events observed by him/her or reported by the subject during the trial.

6.1 Definitions

6.1.1 Adverse Event

Any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a trial treatment whether or not considered related to trial treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a trial treatment, whether or not related to the trial treatment.

6.1.2 Serious Adverse Event

Any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening (any event in which the participant was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization; In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE;
- Results in persistent or significant disability/incapacity; the term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption;
- Is a congenital anomaly/birth defect; or

- Is a medically important event.

Note: Medical and scientific judgment should be exercised in deciding which is a medically important event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse. A "suspected transmission of infectious agent by a medicinal product" is also considered a serious adverse event under the SAE criterion "Other medically important condition".

6.2 Attribution/Causality

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product).

- The investigator is obligated to assess the relationship between trial treatment and each occurrence of each AE/SAE.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor/designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor/designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

Table 3 Adverse Event Attribution/Causality Ratings

Relatedness Rating	Definition
Not Related	An adverse event, which is not related to the use of the drug.

Relatedness Rating	Definition
Unlikely	An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s) or concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.
Possible	An adverse event, which might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s) or concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
Probable	An adverse event, which might be due to the use of the drug. The relationship in time is suggestive, e.g., confirmed by dechallenge. An alternative explanation is less likely, e.g., concomitant drug(s) or concomitant disease(s).
Certain	An adverse event, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s) or concomitant disease(s).

Table 4 Definitions for Adverse Event Severity Gradings

Grade	Severity Rating	Definition
GRADE 1	Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4	Potentially Life-Threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

See Appendix 2 for full DMID Toxicity Tables. The above ratings should be used to estimate the grade for abnormalities NOT found elsewhere in the Toxicity Tables. Lab results within the testing facility's normal range will not be considered AEs when referenced to the DMID assessment/grading scale (Appendix 2).

Laboratory abnormalities and cardiovascular findings of hypertension or hypotension Grade 2 or above on the DMID toxicity tables will be considered AEs.

6.3 Reporting

6.3.1 Adverse Event

Adverse Events will be collected by the Investigator or qualified designee(s) from the time a subject signs the Informed Consent Form through the follow-up phone calls (Day 11+1 day). Any AE (serious or non-serious) observed by the Investigator (or a

suitably medically qualified designee) or reported by the subject will be recorded on the Adverse Event Case Report Form. The Investigator will review each AE and assess its relationship to drug treatment based on all available information at the time of the completion of the CRF. The following information will be recorded for each Adverse Event reported:

- Diagnosis of the AE, if possible. In the case where an overall diagnosis cannot be made, each specific sign and/or symptom will be recorded as individual AEs;
- Date of onset;
- Stop date (with duration, if applicable);
- Severity;
- Action taken with IMP;
- Other action taken;
- Outcome;
- Relationship to IMP;
- Occurrence;
- Seriousness

6.4 Serious Adverse Event Reporting

The Investigator or designee will notify the appropriate Sponsor contact immediately after the SAE detection, observation, or report of occurrence (regardless of the relationship to test article). The Sponsor contact information for SAE reporting is provided below:

PPD PVG (pharmacovigilance service provider for TB Alliance)
Email: rtpsafety@ppdi.com
Safety Hotline: +1 888 483 7729
Safety Fax Number +1 888 529 3580

And

Antonio (Tony) Lombardi, MD
Global Alliance for TB Drug Development
40 Wall Street, 24th Floor
New York, NY 10005, United States of America
Telephone: +1 646.616.8681
Mobile: +1 917.601.0024
Facsimile: +1 212.227.7541
Email: Antonio.Lombardi-Consultant@tballiance.org

These SAE reports must contain the following information:

A. Study name/number (for EU also the Eudract number)

B. Study drug
C. Investigator details (name, phone, fax, e-mail)
D. Subject number
E. Subject demographics
F. Clinical event:
    1) Description
    2) Date of onset
    3) Treatment (drug, dose, dosage form)
    4) Adverse event relationship to study drug
    5) Action taken regarding study drug in direct relationship to the AE
G. If the AE was fatal or life-threatening
H. If applicable, cause of death (whether or not the death was related to study drug)
I. If applicable, autopsy findings (if available)

Any new SAE that occurs within one month after the study period and is considered to be possibly related to the Investigational Product (IP) should be recorded and reported immediately to the Sponsor.

The person responsible for the study shall take care that the study has been carried out in accordance with pharmacovigilance local regulations.

All serious event reporting will adhere to U.S. Code of Federal Regulations (21 CFR Part 312.32) for IND drugs and 21 CFR 314.80 for marketed drugs (15-day alerts). The Institutional Review Board (IRB) will be notified of the alert reports per Food and Drug Administration (FDA) regulations.

All AEs, including SAEs, will be followed to resolution when possible. All AEs and treatment administered will be recorded on the case report form (CRF).

The Sponsor will be responsible for processing and reporting any SAEs (and their relevant updates) to the FDA or other applicable regulatory agency.

6.5 Follow up of Adverse Events

All AEs will be followed until:

- Satisfactory clinical resolution or stabilization; or
- End of the follow-up period; and
- All queries on these AEs have been resolved.

Certain long-term AEs cannot be followed until resolution within the setting of this protocol. In these cases, follow-up will be the responsibility of the treating physician. However, this will have to be agreed upon with the Sponsor Medical Monitor.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. Investigator should contact sponsor/designee to discuss appropriate medical follow-up if consultation required.

If a participant dies during participation in the trial or during a recognized follow-up period, the investigator will provide sponsor/representative with a copy of any post-mortem findings including histopathology.

New or updated information on an SAE will be recorded in the originally completed CRF and submitted to sponsor within 24 hours of the information becoming known per SAE reporting guidelines.

6.6 Post-Trial Serious Adverse Events

Any new SAEs reported by the subject to the Investigator that occur up to 30 days after last contact and are determined by the Principal Investigator to be possible, probable or very likely related to the use of the IMP, will be reported to the Sponsor, IRB and FDA on an expedited basis as required in accordance with local requirements and ICH guidelines for GCP.

6.7 Clinical Laboratory Adverse Events

Changes in the results of the Clinical Laboratory assessment results which the Investigator feels are clinically significant will be reported as adverse events. It is the Investigators' responsibility to review the results of all laboratory tests as they become available. This review must be documented by the Investigators' dated signature on the laboratory report. For each abnormal laboratory test result, the Investigator needs to ascertain and document if this is a clinically significant change from baseline for that individual participant. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is determined by the Investigator to be a clinically significant change from baseline for that participant, it is considered to be an adverse event.

6.8 Drug Interaction

If the Investigator becomes aware that the subject has experienced a drug interaction which has resulted in an adverse event, it will be recorded as an adverse event.

6.9 Pregnancy

The Investigator will immediately notify the Sponsor of any pregnancy that is discovered during the clinical trial. Pregnancy forms will be completed for all pregnancies reported during the study or in the 30 days after completion of the IMP. In addition, the Investigator will report to the Sponsor follow up information regarding the outcome of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for 6 months.

If pregnancy is suspected while the subject is receiving IMP, the IMP will be withheld immediately until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner and the subject withdrawn from the trial. Protocol-required procedures for trial discontinuation and follow up will be performed unless contraindicated by the pregnancy.

If the Investigator becomes aware the female partner of a male subject becomes pregnant during the study or in the 30 days after the completion of IMP, consent will be requested from the female partner for collection of information on her pregnancy history and for information on the current pregnancy and birth.

7 GENERAL CONSIDERATIONS

7.1 Basic Principles

This research will be carried out in accordance with the protocol, the International Council for Harmonisation (ICH), Guideline for Good Clinical Practice: Consolidated Guidance (E6), and applicable regulatory requirements(s) including clinical research guidelines established by the Basic Principles defined in the U.S. 21 CFR Parts 50, 56, and 312 and the principles enunciated in the Declaration of Helsinki (revised version Fortaleza 2013).

7.2 Institutional Review Board

This protocol will be reviewed by an appropriate IRB and study enrollment will not commence until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the principles and requirements described in 21 CFR Part 56.

7.3 Informed Consent

Written informed consent will be obtained from each subject before performing any baseline study-specific evaluations. The informed consent document is prepared by the Investigator or designee, subject to review and approval by the Sponsor, and forwarded to a qualified IRB for final review and approval. The IRB-approved document must contain, at minimum, the eight basic elements of informed consent. Only the most

recently IRB-approved Informed Consent Document must be used to consent prospective study subjects. One copy of the signed and dated informed consent document will be given to the subject and the original retained by the Investigator/site.

7.4 Indications for Subject Withdrawal

Subjects will be free to withdraw at any time for any reason, or they may be withdrawn if necessary, to protect their health and safety or the integrity of the study data.

Subjects who are withdrawn from the study will not be replaced. Subjects in Panel 1 (fed) who do not complete the required FDA standard high-fat, high-calorie breakfast will be withdrawn from that study period.

The final report will include reasons for withdrawals. In the event of an early termination, subjects will undergo the procedures described in Section 5.7.

7.5 Termination of the Study

The Principal Investigator reserves the right to terminate the study in the interest of subject safety and welfare. The Sponsor reserves the right to terminate the study at any time for administrative reasons.

7.6 Documentation

All documents pertaining to the study, including a copy of the approved protocol, copy of the informed consent document and Health Insurance Portability and Accountability Act (HIPAA) documents, completed CRFs (where applicable), drug accountability and retention records, and other study related documents will be retained in the permanent archives of the study site. These will be available for inspection at any time by the Sponsor or the FDA. Per 21 CFR 312, record retention for this study is required for a period of two years following the date on which this study agent is approved by the FDA for the marketing purposes that were the subject of this investigation; or, if no application is to be filed or if the application is not approved for such indication, until two years following the date on which the entire study is completed, terminated, or discontinued, and the FDA is notified.

Subject records will be kept private except when ordered by law. The following individuals will have access to study subject records: Principal Investigator and designees, study Sponsor, monitors, and auditors, the FDA, other government offices, and the IRB.

7.7 Trial Monitoring

Sponsor personnel (or designees) will be responsible for monitoring the study to ensure compliance with the protocol and GCP. Compliance may be verified by one or more of the following methods: on-site visits, frequent communication with the Investigator,

and/or review of CRFs and source documents. The Investigator agrees to permit such monitoring as well as audits or reviews by regulatory authorities and the IRB.

7.8 Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

8 PHARMACOKINETIC ANALYSIS

8.1 Analytical Methodology

Plasma samples will be analyzed for pretomanid using a validated assay. The samples from all evaluable subjects completing at least one study period will be analyzed. Samples from subjects who experience emesis within 4 hours of dosing will not be analyzed.

8.2 Pharmacokinetic and Statistical Analyses

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

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

Descriptive statistics will be used to summarize pretomanid plasma concentrations at each sampling time point and for derived plasma PK parameters, as applicable. Statistics include sample size (n), mean, SD, percentage coefficient of variation (%CV), geometric mean, median, minimum, and maximum.

For each participant, pretomanid plasma concentration-time data will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. Additionally, pharmacokinetic parameters may be explored graphically.

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

The effect of dose on the relative bioavailability of the dispersible tablet will be determined separately for each panel using the same model as above.

The effect of food on the relative bioavailability of pretomanid will be determined comparing, across panels, each formulation and dose taken after eating breakfast versus

the same formulation and dose taken in fasted conditions using a mixed model with the log transformed PK parameter as response variable; panel, sequence, period, treatment, and panel-by-treatment interaction as fixed effects; and participant as random effect.

The T_{max} of pretomanid for each of the formulations will be descriptively compared.

Other statistical models and/or population pharmacokinetic modelling may also be used for further data interpretation.

Pharmacokinetic calculations will be performed using appropriate software.

9 FACILITIES

CLINICAL TRIAL SITE

Worldwide Clinical Trials Early Phase Services, LLC
2455 N.E. Loop 410, Suite 150
San Antonio, Texas 78217
Telephone: 210.635.1500
Fax: 210.635.1646

CLINICAL LABORATORIES

Worldwide Clinical Trials Early Phase Services, LLC
2455 N.E. Loop 410, Suite 150
San Antonio, Texas 78217
Telephone: 210.635.1500
Fax: 210.635.1646

ANALYTICAL LABORATORY

Alliance Pharma, Inc.
Project Manager: Michelle Black
Contact for Sample Shipment: Anna Cucinotta
17 Lee Boulevard
Malvern, PA 19355
Phone: 610.296.3152
Fax: 610.296.3153
Email: samples@alliancepharmaco.com
Web: www.alliancepharmaco.com

CLINICAL MONITOR

Michelle Behnke, CCRA
Sr Clinical Research Associate Consultant, TB Alliance
Phone: 512.592.1080

Email: michelle.behnke-consultant@tballiance.org
DATA MANAGEMENT AND STATISTICS

Worldwide Clinical Trials, Ltd
1st Floor, Waterfront House
Beeston Business Park
Beeston, Nottingham
NG9 1LA, UK
Telephone: +44(0)115.956.7711
Fax: +44(0)115.922.0960

10 DRUG SUPPLIES

TB Alliance will supply sufficient quantities of all study drug formulations to allow completion of this study.

Study drug formulations will be shipped to Worldwide Clinical Trials Early Phase Services, LLC pursuant to site standard operating procedures. Upon receipt of the study drug products, the supplies will be inventoried and stored in an environmentally controlled and secure, limited access area. The lot numbers of the drugs along with the expiration dates (where available) will be recorded and copies of the Certificate of Analysis (where available) will be maintained on file. Records will be maintained of the receipt and dispensation of the drugs supplied.

Sufficient quantities of study drug will be supplied to allow for retention samples. Retention samples will be stored at the clinical site pursuant to the site SOPs. The site will be responsible for randomly selecting doses to be administered and doses to be retained. At the conclusion of the study, any unused study drug (not including retention samples) will be returned to the sponsor or destroyed by the site pursuant to written authorization by the sponsor and applicable federal and state regulations.

11 ADMINISTRATIVE ISSUES

The Investigator is referred to the Investigator Brochure for pretomanid (PA-824)[1], information provided during the study initiation visit, and ICH Guidelines for Good Clinical Practice for information regarding the study drug, details, or general considerations to be followed during the course of this study.

12 EVENTS SCHEDULE

Table 5 Schedule of Assessments and Procedures

	SCR	Confinement (To Day 26)																						
STUDY PERIOD	-21 to -1		Session 1					Break	Session 2					Break	Session 3					Break	Session 4					
STUDY DAY		-1	1	2	3	4	5	6-7	8	9	10	11	12	13-14	15	16	17	18	19	20-21	22	23	24	25	26	33 or early withdrawal
Written informed consent and medical history	X																									
Updated medical history		X																								
Height	X																									
Weight	X	X																								
Physical examination[a]	X	X																								X
Vital signs (blood pressure, pulse, temperature, respiration rate, and pulse oximetry)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[c]	X	X	X						X						X						X					X
HIV, hepatitis B surface antigen and hepatitis C	X																									
Clinical laboratory tests (hematology, chemistry and urinalysis)[d]	X	X					X						X						X						X	X
Urine drug/cotinine/alcohol test	X	X																								X
Serum pregnancy test (females)	X	X																								
Urine pregnancy test (females)																										X
FSH (postmenopausal women)	X																									
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dosing[f]			X						X						X						X					
Pharmacokinetic blood collection[g]			X	X	X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	

a. Physical Examination: Full physical examination at screening and abbreviated physical examination at check-in. Height will only be collected at screening,
b. Vital Signs: Measured at check-in and while participants are confined to the clinic (once per day or as otherwise needed [determined by the Investigator]). Vital signs will be measured within 90 minutes prior to dosing and within 15 minutes of the remaining defined timepoints. Both blood pressure and heart rate (pulse) should be captured simultaneously. Blood pressure and heart rate should be measured after participants are in a seated position for at least 2 minutes and then again after standing for 1 minute, except when they are supine or semi-reclined because of study procedures and/or adverse events, or as deemed necessary by the Investigator.
c. ECG: 12-lead safety ECGs will be printed and reviewed on-site by the Principal Investigator or designee. Single ECGs will be obtained at screening and on Study Days 1, 8, 15 and 22 and must be performed within 2 hours prior to dosing and completed 20 minutes prior to predose blood draw.
d. Laboratory Safety Assessments: Haematology: haemoglobin, haematocrit, total and differential leukocyte count, red blood cell count, and platelet count. Serum chemistry: albumin, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate transaminase, alanine transaminase, sodium, potassium, chloride, lactate dehydrogenase, calcium, uric acid, glucose, gamma-glutamyl transferase, and magnesium. Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocyte esterase and urobilinogen. If protein, occult blood, nitrite or leukocyte esterase values are out of range, a microscopic examination will be performed.
e. Adverse Events (AEs): Participants will be monitored for AEs from the time of signing the informed consent document and throughout the study via safety assessments, observation, and participant reporting. A specific inquiry regarding adverse events will be conducted prior to dosing and at timepoints determined by the Investigator post-dose and upon return to clinic for subsequent visits.
f. Investigational Medicinal Product (IMP) Administration: See Figure 1.
g. Pharmacokinetic (PK) Sampling: 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 intake). Duplicate samples will be collected for all plasma pharmacokinetic samples.

13 REFERENCES

1. Investigator's Brochure for Pretomanid (PA-824); Version 19, 02 October 2019; Global Alliance for TB Drug Development.
2. WHO. Global TB Report. 2018a.
3. WHO. Global TB Report. 2012.
4. Luna, JAC. A tuberculosis guide for specialist physicians (International Union against Tuberculosis and Lung Disease). 2004.
5. Centers for Disease Control and Prevention (2013). Fact Sheet. Trends in Tuberculosis, 2012." Atlanta, GA: U.S. Department of Health and Human Services, CDC, September 2013.
6. "Common Terminology Criteria for Adverse Events (CTCAE) version 5.0" U.S. Department of Health and Human Services November 2017.
7. "Guidance For Industry: Statistical Approaches to Establishing Bioequivalence" U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) January 2001.
8. "Guidance For Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations" U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) March 2003.

APPENDIX 1 PHARMACOKINETIC SAMPLE COLLECTION, PROCESSING, AND SHIPMENT INSTRUCTIONS

A. Collection and Processing

A more detailed description of plasma sample preparation requirements may be provided by the analytical laboratory. If such a description is provided, the method of sample preparation provided by the laboratory shall supersede those provided in this protocol and appropriate documentation shall be placed in the Investigator Site File (ISF).

Processing Instructions	
1	Blood samples will be collected into 2.0 mL Vacutainer tube(s) containing K_2-EDTA. The time and date of collection for each sample will be recorded.
2	During each treatment period, samples will be collected at 0 hour (predose, within 60 minutes before the dose of study drug), and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours postdose. (Note: Predose blood samples obtained from backup subjects who are randomized into the study may exceed the predose collection window.)
3	Blood samples will be centrifuged at approximately 3000 rpm for 10 minutes at approximately 4 degrees Centigrade.
4	The resulting plasma samples will be harvested and transferred in approximately equal aliquots into two appropriately labeled polypropylene screw-cap tubes.
5	Samples will be placed in an upright position in a freezer at approximately -20 degrees Centigrade within 60 minutes of collection.
6	Samples will remain frozen until assayed.

Sample Collection Summary					
Number of subjects	Number of time points per period	Number of periods	Sample type	Tube type	Number of tubes per time point
48	15	4	Collection	2.0 mL K_2EDTA Vacutainer	1
			Aliquot	600 uL Polypropylene screw Cap	2

B. Labeling of aliquot tubes

Labels will contain at least the following information:

a) Study number

b) Subject identification

c) Period or dosing phase; sampling time (relative to dosing)

d) Aliquot letter (a or b)

C. Shipment

1. The samples will be transferred to the analytical laboratory after completion of the study or at mutually agreed upon time points during the clinical conduct of the study. The second set of samples will be shipped after the bioanalytical laboratory confirms receipt of the first set of samples.
2. Samples will be packaged into cryoboxes and sorted by subject
3. Before shipment, the samples will be appropriately packed in a cooler containing dry ice. Sufficient dry ice will be added to ensure that the samples will remain frozen for at least 72 hours.
4. An electronic manifest will be provided in advance. The shipment will be accompanied by documentation containing the following information: name of the study drug product, protocol number, number of subjects, and number of samples included in the shipment. Expected samples that are not present will be identified.
5. All frozen pharmacokinetic samples will be transferred with accompanying documentation to:

   Alliance Pharma
   17 Lee Boulevard
   Malvern, Pennsylvania 19355
   Telephone: 610.296.3152
   Contact name: Michelle Black
   Email: samples@alliancepharmaco.com
   mblack@alliancepharmaco.com

APPENDIX 2 DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASE TOXICITY TABLE

Division of Microbiology and Infectious Disease (DMID) Toxicity Table

Source: U.S. National Institute of Allergy and Infectious Diseases, DMID, November 2007 (Draft)

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

Grade	Severity Rating	Definition
GRADE 1	Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required.
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4	Potentially Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of Patients in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.

- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supersede the use of these tables for specified criteria.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/ mm^3	13,000-15,000 /mm^3	15,000-30,000/mm^3	>30,000 or <1,000 /mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (non-fasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria*	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

*Assessment does not apply if a subject is on menses.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment[1]	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required[1]	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

1) For protocol TBI-223-CL-001, defined as increase from baseline in predose vital signs.

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	Transient - no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator;FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea	moderate or persistent; 5-7 loose stools/day or	>7 loose stools/day or bloody diarrhea; or orthostatic	hypotensive shock or physiologic consequences

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
	last < 1 week	diarrhea lasting >1 week	hypotension or electrolyte imbalance or >2L IV fluids required	requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	Subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint distruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25- 50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

Protocol Clarification Letter

TB Alliance, Protocol Pa-824-CL-011, 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 purpose of this letter is to clarify the that retention samples are not needed.

The section of protocol version 1.0 dated 06 Dec 2019 affected by this change is indicated below.

Protocol Page 26, Section 10, Drug Supplies, Paragraph 3:

Currently reads:

Sufficient quantities of study drug will be supplied to allow for retention samples. Retention samples will be stored at the clinical site pursuant to the site SOPs. The site will be responsible for randomly selecting doses to be administered and doses to be retained. At the conclusion of the study, any unused study drug (not including retention samples) will be returned to the sponsor or destroyed by the site pursuant to written authorization by the sponsor and applicable federal and state regulations.

Revised to read:

Retention samples of the investigational study drug will not be required. At the conclusion of the study, any unused study drug will be returned to the sponsor or destroyed by the site pursuant to written authorization by the sponsor and applicable federal and state regulations.

Approved By:

Sponsor Contact:

Frances Pappas
TB Alliance
40 Wall Street, 24th Floor
New York, NY 10005
Phone: 646.616.8664

DocuSigned by:
Fran Pappas
Signer Name: Fran Pappas
Signing Reason: I have reviewed this document
Signing Time: 11-Dec-2019 | 11:39:20 EST
A865E5618B934A6AAC744B71EBB852B4

(Signature) (Date)

Medical Officer:

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TB Alliance
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Signer Name: Antonio Lombardi
Signing Reason: I approve this document
Signing Time: 11-Dec-2019 | 08:20:47 PST
AAFDCEAAD2874D3382507893E2EDC27C

(Signature) (Date)

Principal Investigator:

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Signing Reason: I approve this document
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FA8D8484FD8647B3A4A33071357CA7F7

(Signature) (Date)

Protocol Clarification Letter 2

TB Alliance, Protocol Pa-824-CL-011, 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 purpose of this letter is to clarify two exclusion criteria and add a taste evaluation postdose.

The section of protocol version 1.0 dated 06 Dec 2019 affected by this change is indicated below.

Protocol Page 6, Section 4.2, Exclusion 2:

Currently reads:

A clinically significant abnormal finding on the physical examination, medical history, electrocardiogram (ECG), or clinical laboratory results.

Revised to read:

A clinically significant abnormal finding on the physical examination, medical history, electrocardiogram (ECG), or clinical laboratory results **(e.g., laboratory profiles are normal up to and including Grade 1 per DMID toxicity tables).**

Protocol Page 6, Section 4.2, Exclusion 7:

Currently reads:

Use of any over-the-counter (OTC) medication (including nutritional or dietary supplements, herbal preparations, or vitamins) within 7 days before the first dose of study medication until the end of study visit without evaluation and approval by the Investigator. Up to 3 grams per day of acetaminophen is allowed at the discretion of the Investigator prior to dosing.

Revised to read:

Use of any over-the-counter (OTC) medication (including nutritional or dietary supplements, herbal preparations, or vitamins) within 7 days before the first dose of study medication until the end of study visit without evaluation and approval by the Investigator. **Occasional use of** up to 3 grams per day of acetaminophen is allowed at the discretion of the Investigator prior to dosing.

Protocol Page 27, Section 12, Table 5 Schedule of Assessments and Procedures:

Add "Taste evaluation[h]" to Table 5 with the following footnote:

h. Taste evaluation will be conducted immediately after dosing and 5 minutes after administration to determine any after taste.

Approved By:

Sponsor Contact:

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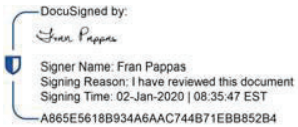
TB Alliance
40 Wall Street, 24th Floor
New York, NY 10005
Phone: 646.616.8664



(Signature) (Date)

Medical Officer:

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Principal Investigator:

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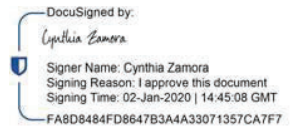

(Signature) (Date)

Protocol Clarification Letter 3

TB Alliance, Protocol Pa-824-CL-011, 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 purpose of this letter is to update the contact information for serious adverse event (SAE) reporting. The section of protocol version 1.0 dated 06 Dec 2019 affected by this change is indicated below.

Protocol Page 19, Section 6.4, Serious Adverse Event Reporting:

Currently reads:

PPD PVG (pharmacovigilance service provider for TB Alliance)
Email: rtpsafety@ppdi.com
Safety Hotline: +1 888 483 7729
Safety Fax Number: +1 888 529 3580

And

Antonio (Tony) Lombardi, MD
Global Alliance for TB Drug Development
40 Wall Street, 24th Floor
New York, NY 10005, United States of America
Telephone: +1 646.616.8681
Mobile: +1 917.601.0024
Facsimile: +1 212.227.7541
Email: Antonio.Lombardi-Consultant@tballiance.org

Revised to read:

TB Alliance Pharmacovigilance
Email: AE_inbox@tballiance.org

Questions relative to SAE case processing may also be sent to the above-mentioned email address. If there is ever an email failure upon trying to report an SAE, please call Dr. Lombardi at 1-917-601-0024 and he will notify the Safety team at TB Alliance.

Medical questions relative to AEs or SAEs can be directed to:
Antonio (Tony) Lombardi, MD
Global Alliance for TB Drug Development
40 Wall Street, 24th Floor
New York, NY 10005, United States of America
Telephone: +1 646.616.8681
Mobile: +1 917.601.0024
Facsimile: +1 212.227.7541
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Approved By:

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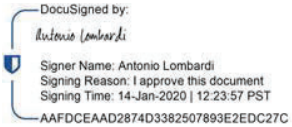

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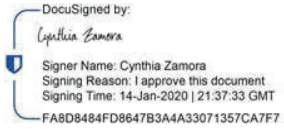

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