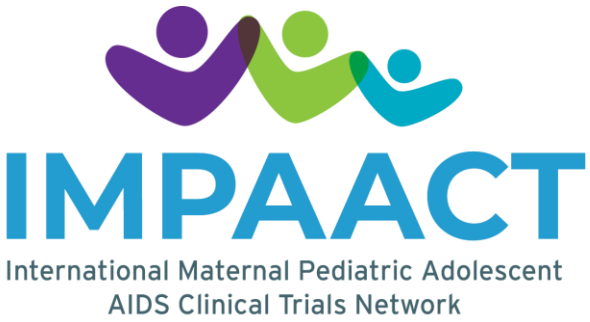

IMPAACT 2034

Phase I Study of the Pharmacokinetics, Safety, and Acceptability of a Single Dose of Pretomanid Added to an Optimized Background Regimen in Children with Rifampicin-Resistant Tuberculosis

IND#: 158,882
DAIDS ES # #38754

This file contains the current IMPAACT 2034 protocol, which is comprised of the following documents, presented in reverse chronological order:

- Letter of Amendment #1, dated 22 December 2022
- Protocol Version 1.0, dated 15 July 2022

Letter of Amendment #1 for:

IMPAACT 2034
Phase I Study of the Pharmacokinetics, Safety, and Acceptability of a Single Dose of Pretomanid Added to an Optimized Background Regimen in Children with Rifampicin-Resistant Tuberculosis

Version 1.0, dated 15 July 2022

DAIDS Study ID #38754
IND #158,882 Held By NIAID/DAIDS

Letter of Amendment Date: 22 December 2022

Table of Contents

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) affects the IMPAACT 2034 study, including the study informed consent forms, and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for their review and approval. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All applicable IRB/EC and regulatory entity requirements must be followed.

For sites that were activated to initiate the study prior to issuance of this LoA, upon obtaining all required IRB/EC and regulatory entity approvals, each site should immediately begin implementing this LoA. Sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA. Unless otherwise specified by site IRBs/ECs or other regulatory entities, no re-consenting of participants enrolled in the study prior to approval of this LoA is required after approval of this LoA.

For sites that were <u>not</u> activated to initiate the study prior to issuance of this LoA, upon obtaining all required IRB/EC and regulatory entity approvals, sites are required to submit an LoA registration packet to the DAIDS PRO at the RSC. Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. However, activation may occur following receipt of all required IRB/EC and regulatory entity approvals for protocol Version 1.0 only with completion of all other study activation requirements and receipt of a site-specific study activation notice from the IMPAACT Operations Center.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential document files for IMPAACT 2034. If the IMPAACT 2034 protocol is amended in the future, applicable contents of this LoA will be incorporated into the next version of the protocol.

IMPAACT 2034
Phase I Study of the Pharmacokinetics, Safety, and Acceptability of a Single Dose of Pretomanid Added to an Optimized Background Regimen in Children with Rifampicin-Resistant Tuberculosis

DAIDS Study ID #38754

Version 1.0, Letter of Amendment #1
Letter of Amendment Signature Page

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Council on Harmonisation Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Signature of Investigator of Record	Date
Name of Investigator of Record (printed)	

Summary of Modifications and Rationale

The primary purpose of this LoA is to incorporate modifications as recommended by the US Food and Drug Administration (FDA). Other updates are included to the protocol team and study site rosters to reflect current membership and to the clinical site monitoring directions for consistency across IMPAACT protocols. The procedural recommendations received from the FDA, shown in the Implementation section below, serve to:

- *Defer enrollment of neonates until additional pediatric safety and pharmacokinetic data are available:* The Paediatric Investigation Plan with the European Medicines Agency includes as a key binding element an age requirement of less than 18 years of age without a lower age limit; however, the US FDA highly recommended the staggering of enrollment to inform safety assessments following finalization of Protocol Version 1.0. This LoA incorporates that FDA recommendation to stagger enrollment, with deferred enrollment of neonates (defined as children who are 28 days of age or younger [≤28 days of age]) until safety and pharmacokinetic data are available in heavier (and older) groups.

- *Revise requirements for pregnancy testing:* Based on the available prior research, the protocol team originally opted to include pregnancy testing only at screening and not require testing on the day of enrollment. As noted in protocol Section 1.2.2, no mutagenic or clastogenic effects were detected in both an in vitro bacterial reverse mutation assay and an in vitro mammalian chromosome aberrations assay using a Chinese hamster ovary cell line. Pretomanid showed no clastogenicity in a mouse bone marrow micronucleus assay. In addition, preclinical toxicology studies in rats showed that pretomanid was not teratogenic, and no peri-postnatal effects occurred at doses that did not also produce maternal toxicity in rats. However, the protocol is revised as below to require that specimens for the screening pregnancy test be collected within five days prior to enrollment and an additional pregnancy test will be performed at the Week 2 visit, with referral to appropriate non-study care and treatment, consistent with protocol Section 8.3.2. The five-day window prior to Entry would minimize the potential chance that the participant would be enrolled into the study while pregnant, particularly as many participants will be recruited from hospital settings and unlikely to have any potential pregnancy chances during this time.

Implementation

Modifications of protocol text are presented below, generally in order of appearance in the protocol. Where applicable, modified text is shown using strikethrough for deletions and bold type for additions.

1. To reflect current protocol team membership, Kacey Matecki and Adelaide Amo-Mensah are removed from the protocol team roster (deletion not shown). Marisa Guptarak, Dean Soko, CaTiffaney Griswould, and Lassallete Canada are added. Marisa Guptarak is also added as a Clinical Research Manager on the protocol cover page.

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2. To reflect current study site membership, Megan Palmer and Mapule Mosidi are removed from the study site roster (deletions not shown). Louvina van der Laan and Ingrid Courtney are added.

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3. Schema, Study Population (added) second paragraph:

Neonates (defined as children who are 28 days of age or younger [≤28 days of age]) may be allowed to enroll after evaluation of data for the interim analysis (see Sections 9.5.1-9.5.2). Study drug dosing for neonates will follow the same weight-based dose as noted below.

4. Consistent with the updates in protocol Section 6, and for ease of reference and implementation, Figure 1 is updated as shown (with revisions incorporated) on page 10 of this LoA.

5. Section 1.3.2, Rationale for Selected Study Population, fifth, sixth, and seventh (added) paragraphs:

Following finalization of Protocol Version 1.0, the FDA highly recommended the staggering of enrollment to inform safety assessments. The protocol team noted the FDA guidance to consider staggering enrollment based on age (or weight) in pediatric studies, if there are safety or risk considerations that might be different by age or weight. (34a) However, there are no known or potential developmental or other safety concerns for pretomanid, based on either weight or age, in the female population to be enrolled in IMPAACT 2034. Rigorous pharmacometric modeling of data from studies of pretomanid in adults has been applied to scale dosing to children so that their exposures are expected to be in the range experienced by adults at the marketed dose (as described in Section 10.3.1). Pretomanid-containing regimens for rifampicin-resistant tuberculosis are now routinely recommended as first-line treatment in adults and in adolescents aged 15 years and older by the World Health Organization (WHO) and are routinely given in programmatic settings.

Enrollment of neonates in IMPAACT 2034 is unlikely given the eligibility criteria; it is also anticipated, based on site enrollment projections and prior experience in other similar IMPAACT studies in children with drug-resistant TB, that enrollment of children in lower weight groups will be slower than enrollment of those in higher weight groups. Based on numerous factors, including the highly favorable safety and efficacy results from pretomanid-based regimens in TB PRACTECAL and ZeNix adult trials, the proposed single-dose study design, and the lack of safety signals in female individuals (to whom enrollment will be restricted) in the accumulated meaningful human safety database, the protocol team recommended, and the FDA agreed, to avoid an age- or weight-de-escalation approach in the

overall study design to maintain the overall enrollment timeline and provide data to support the continued development of pretomanid for use in children. This is consistent with the FDA guidance on pediatric antiretroviral development (34b), which emphasizes the importance of enrolling cohorts in parallel rather than in series, and consistent with the FDA guidance on enhancing the diversity of clinical trial populations. (34c) In other TB studies in children, a de-escalation approach has previously significantly delayed information about therapeutics in children. Equity in time to evidence for children about the safe and effective use of life-saving compounds is essential. (34d) The multiple delays in evidence for the youngest or smallest children (with the highest number of quality-adjusted life years remaining to them and higher case-based mortality based on age-related risk from disseminated TB) places an ethical premium on minimizing further delays in the generation of high-quality evidence.

In response to the FDA comments, the protocol is revised to defer enrollment of neonates until safety and pharmacokinetic data are available in older groups. The safety and PK data assessment will be completed as part of the planned interim analysis, as described in Sections 9.5 and 10.4.

6. Section 3, Study Design, first paragraph, second sentence:

   The term children is used within the protocol to indicate the total age range from infants through adolescents; as noted in Section 1.3, enrollment will be limited to children assigned female sex at birth **and enrollment of neonates will be deferred until safety and pharmacokinetic data are available in older groups, pending review by the CMC and SMC during the interim analysis.**

7. Section 3, Study Design, fourth paragraph:

   The Protocol Team will closely monitor the number of participants confirmed to meet the above-listed definitions. Participants who are not confirmed as evaluable will not be counted toward the study accrual quotas but will be retained on-study and included in primary and secondary analyses, unless otherwise specified in Sections 9 and 10. **The CMC will also closely monitor accrual into each weight group and may pause and subsequently close or resume accrual into groups, particularly prior to the interim analysis, up to the target number evaluable for each group (as described further in Section 9.5.1).**

8. Section 3, Study Design, fifth paragraph, fourth sentence:

   The results of this analysis, as well as all available PK and safety data, will be reviewed by the Clinical Management Committee (CMC) and the IMPAACT Study Monitoring Committee (SMC) to determine whether the current sample size of nine evaluable participants per group is sufficient or if the sample size should be increased for any of the four groups to achieve the study objectives**; the results of the analysis will also inform whether safety data are acceptable to allow enrollment of neonates (as described further in Section 9.5)**.

9. Section 4.1.3, Inclusion Criteria, added note:

   Note: Neonates (defined as children who are 28 days of age or younger [≤28 days of age]) may be allowed to enroll after CMC and SMC evaluation of safety and PK data at the interim analysis (see Sections 9.5.1-9.5.2).

10. Section 4.1.14, Inclusion Criteria:

    For participants who have reached menarche or who are engaging in sexual activity (self-reported): not pregnant based on testing performed **within 5 days prior to entry** during the study screening period ~~(i.e., within 28 days prior to entry)~~

11. Section 6.1, Screening Visit, third bullet following third paragraph:

    Pregnancy testing may or may not be required **within 5 days prior to study entry** during the screening period per criterion 4.1.14. When testing is required, a blood or urine test may be performed; results must be available for eligibility determination prior to study entry.

12. Section 6.3, Week 2 Visit, within the procedural table, added row for Laboratory, Blood or Urine:

Laboratory	**Blood or Urine**	***For participants who have reached menarche or who are engaging in sexual activity (self-reported):*** **collect blood or urine for pregnancy test**

13. Section 8.3.1, Contraception and Pregnancy Testing, fourth paragraph:

    Pregnancy testing will be performed among participants who have reached menarche or who are engaging in sexual activity **at Week 2 and** at any time if clinically indicated (i.e., pregnancy is suspected). Pregnancy test results will be entered into eCRFs.

14. Section 9.4.2, Accrual, second paragraph, first sentence:

    There is no planned study accrual pause, including during the interim analysis ~~of PK data~~.

15. Section 9.5.1, Monitoring by the Protocol Team, subsection *Study Progress and Quality of Study Conduct*, second paragraph:

    The Protocol Team will monitor participant accrual based on reports that will be generated at least monthly by the Statistical and Data Management Center (SDMC). The team has developed a study accrual plan that includes site-specific and total enrollment projections over the course of the accrual period, and actual accrual will be monitored relative to these projections. **Across sites, the CMC will closely monitor accrual into each weight group; as needed, the CMC may pause and subsequently close or resume accrual into groups, up to the target number evaluable for each group, particularly prior to the interim analysis. Note, in the interim analysis at least 12 evaluable participants are needed from Groups 1 and 2 and at least an additional 12 evaluable participants from Groups 3 and 4. The CMC may also consider pausing accrual into Group 4 prior to the interim analysis to allow the potential for neonates to enroll in the study following completion of the interim analysis. If the sample size is increased following the interim analysis, the Protocol Team will work with sites to update enrollment projections and overall study timelines to monitor accrual.**

16. Section 9.5.1, Monitoring by the Protocol Team, subsection *Interim Analysis for Sample Size Reassessment*, subsection heading:

    Interim Analysis ~~for Sample Size Reassessment~~

17. Section 9.5.1, Monitoring by the Protocol Team, subsection *Interim Analysis*, second (added) paragraph:

    As part of the interim analysis, the CMC will also review all available safety data from all participants to determine if all available data support a recommendation to the SMC to open enrollment for neonates and to continue study implementation.

18. Section 9.5.2, Monitoring by the SMC, subsection *Interim Analysis*, first and second (added) paragraph:

    Following the CMC's review of interim analysis **results** for **PK, safety, and** sample size reassessment**,** as described above in Section**s** 9.5.1 **and 10.4**, the CMC will prepare a summary report for the SMC. The SMC will then have the option to review the CMC's notification via email or to convene a review before providing a recommendation with respect to the CMC's outcome or assessing next steps for the study.

    Safety will be considered acceptable if the following conditions are met:
    - **The CMC and SMC agree that safety is acceptable based on the data AND**
    - **None of the safety triggers for SMC review included in Section 9.5.2, Participant Safety, have been met prior to the interim analysis; OR if a trigger had been met, that the SMC confirmed that the study may proceed**

    If the CMC and SMC determine that enrollment may be opened for neonates, a Memorandum of Operational Instruction, approved by the CMC, will be distributed to sites.

19. Section 12, Clinical Site Monitoring, second paragraph, fourth, fifth (added), and sixth sentences:

    Site investigators **must** ~~will~~ make available study documents for site monitors to review utilizing a secure platform that is 21 CFR Part 11 compliant. **The DMC has configured Medidata Remote Source Review (RSR) to be available to all sites. If Medidata RSR is not utilized, other** potential platform options include: Veeva SiteVault, Medidata Rave Imaging Solution, ~~Medidata Remote Source Review,~~ site-controlled SharePoint or cloud-based portal, and direct access to electronic medical records.

20. Section 15, References: The following references were added:

    34a. Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population [Guidance Document]. Silver Spring, MD: US Food and Drug Administration (FDA); 2018 [cited 2022 Aug 28]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11r1-addendum-clinical-investigation-medicinal-products-pediatric-population.

    34b. Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. Pediatric HIV Infection: Drug Development for Treatment [Guidance Document]. Silver Spring, MD: US Food and Drug Administration (FDA); 2019 [cited 2022 Aug 28]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-hiv-infection-drug-development-treatment.

    34c. Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER). Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry [Guidance Document]. Silver Spring, MD: US Food and Drug Administration (FDA); 2020 [cited 2022 Aug 28]. Available from: https://www.fda.gov/regulatory-information/search-fda-

guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial.

34d. Nachman S, Ahmed A, Amanullah F, Becerra MC, Botgros R, Brigden G, et al. Towards early inclusion of children in tuberculosis drugs trials: a consensus statement. Lancet Infect Dis. 2015;15(6):711-20.

21. Appendix I: Schedule of Evaluations, row for Pregnancy test and footnote 3 and (added) footnote 6:

Study Visit	Screening	Week 2
Visit Window	*up to 28 days prior to Entry*	*Day 14 ±5 days*
LABORATORY EVALUATIONS		
Pregnancy test[3] [if needed]	[X][6]	**[X]**
Total Blood Volume	4-11 mL	4**-5** mL

3. ~~At screening,~~ Participants who have reached menarche or who are engaging in sexual activity (self-reported) must have ~~a~~ pregnancy test**ing**~~, with results available prior to enrollment~~. Urine (5 mL) or blood (1 mL) tests are acceptable. The total blood volume shown above accommodates collection of 1 mL of blood, if needed.

6. Samples for testing must be collected within 5 days prior to entry during screening and results must be available prior to enrollment.

22. Appendix II: Sample Informed Consent Form for Study Participation, in item 4, "We will ask questions, examine your child, and discuss the study requirements with you," third paragraph:

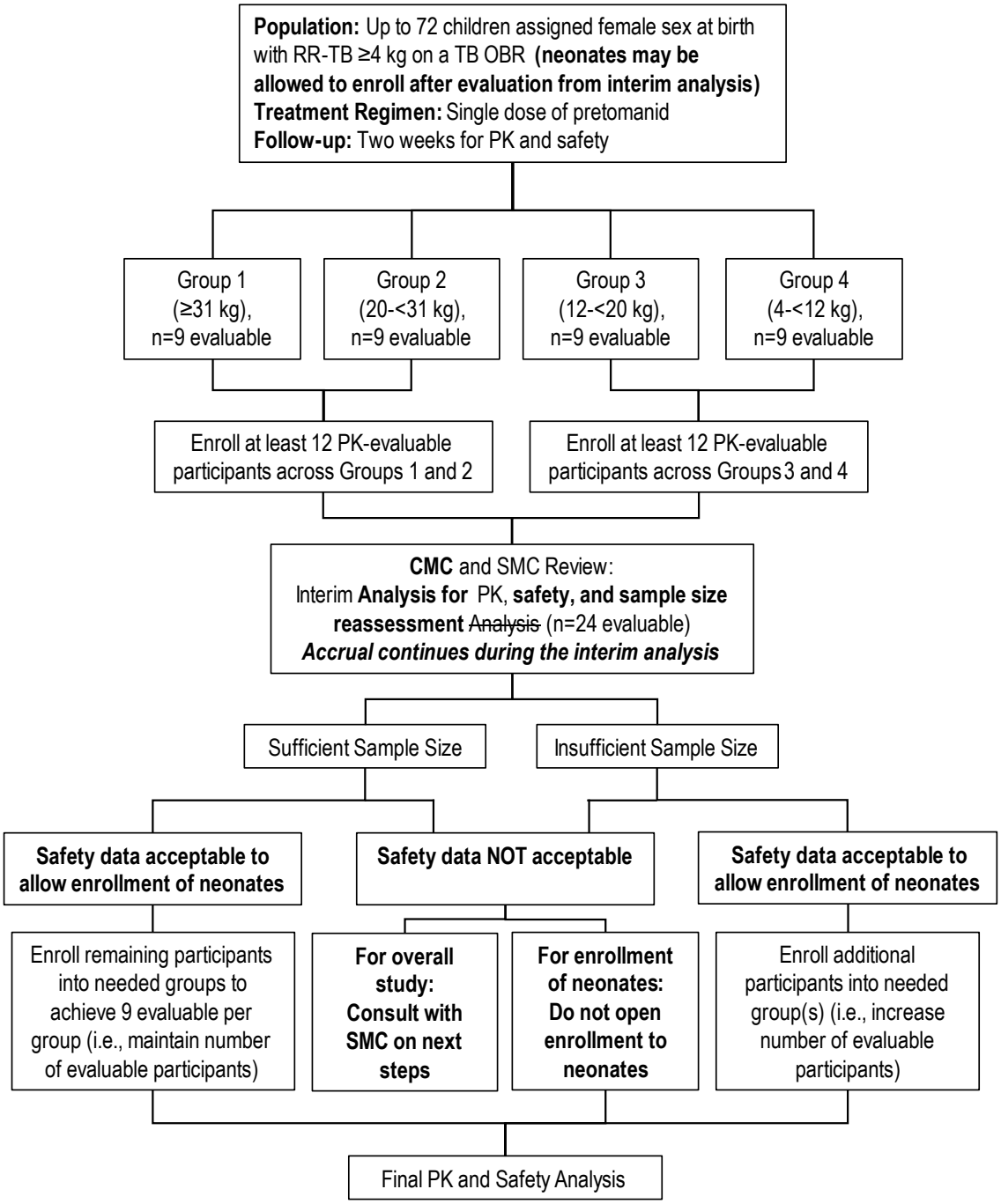
    If your child enters the study and they are sexually active, they will need to agree to use one form of birth control while in the study. **If it is possible for your child to become pregnant, we will also check for pregnancy again about two weeks after your child enters the study.** We will talk to your child about how to prevent pregnancy.

23. Appendix II: Sample Informed Consent Form for Study Participation, in item 8, "After the PK evaluation, your child will have one more visit about 2 weeks after they take pretomanid," fourth bullet point:

    - Draw your child's blood (4**-5** mL or about 1 teaspoon~~s~~) for tests. The tests will check:
      - Your child's blood and blood cells.
      - Your child's liver, kidneys, and other organs.
      - **If it is possible for your child to become pregnant, we will collect blood or urine to check for pregnancy. Children may be tested if they have had their first period or if they are sexually active.**

24. Appendix III: Sample Informed Assent Form for Study Participation, in "What happens in the study," second paragraph, second sentence: Some of the tests done ~~to see if you are eligible~~ for the study include tests for HIV and pregnancy.

Figure 1. IMPAACT 2034 Overview of Study Design



IMPAACT 2034

Phase I Study of the Pharmacokinetics, Safety, and Acceptability of a Single Dose of Pretomanid Added to an Optimized Background Regimen in Children with Rifampicin-Resistant Tuberculosis

A Study of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT)

Sponsored by:
National Institute of Allergy and Infectious Diseases
Eunice Kennedy Shriver
National Institute of Child Health and Human Development
National Institute of Mental Health

Pharmaceutical Support Provided by:
Global Alliance for TB Drug Development (TB Alliance)

DAIDS Study ID #38754
IND #158,882 Held By NIAID/DAIDS

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FINAL Version 1.0
15 July 2022

IMPAACT 2034
Phase I Study of the Pharmacokinetics, Safety, and Acceptability of a Single Dose of Pretomanid Added to an Optimized Background Regimen in Children with Rifampicin-Resistant Tuberculosis

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DAIDS Study ID #38754

Version 1.0
PROTOCOL SIGNATURE PAGE

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Council for Harmonisation Guideline for Good Clinical Practice (ICH E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

_____ _____

Signature of Investigator of Record Date

_____

Name of Investigator of Record
(printed)

IMPAACT 2034
Phase I Study of the Pharmacokinetics, Safety, and Acceptability of a Single Dose of Pretomanid Added to an Optimized Background Regimen in Children with Rifampicin-Resistant Tuberculosis

ABBREVIATIONS AND ACRONYMS

ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-24}	area under the curve from time zero to 24 hours
AUC_{0-48}	area under the curve from time zero to 48 hours
$AUC_{0-\infty}$	area under the curve from time zero extrapolated to infinite time
$AUC_{0-tlast}$	area under the curve from time zero to the last measurable concentration
BID	twice daily
BMI	body mass index
BPa	bedaquiline and pretomanid
BPaL	bedaquiline, pretomanid and linezolid
BPaM	bedaquiline, pretomanid, and moxifloxacin
BPaMZ	bedaquiline, pretomanid, moxifloxacin, and pyrazinamide
BPaZ	bedaquiline, pretomanid, and pyrazinamide
C_{avg}	average serum concentration
C_{max}	maximum concentration
CBC	complete blood count
CDC	(US) Centers for Disease Control and Prevention
CFR	(US) Code of Federal Regulations
CI	confidence interval
CL-	clinical trial with monotherapy [TB Alliance study naming convention]
CL	clearance
CL/F	apparent clearance
CMC	Clinical Management Committee
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRMS	Clinical Research Management System
CRPMC	Clinical Research Product Management Center
CYP3A4	cytochrome P450 family 3 subfamily A member 4
DAERS	(DAIDS) Adverse Experience Reporting System
DAIDS	Division of AIDS
DAIDS AE Grading Table	DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events
DMC	Data Management Center
DNA	deoxyribonucleic acid
DR-TB	drug-resistant tuberculosis
DS-TB	drug-susceptible tuberculosis
EAE	expedited adverse event
EC	ethics committee
ECG	electrocardiogram

eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EIA	enzyme immunoassay
EMA	European Medicines Agency
EMB	ethambutol
F	relative bioavailability
FDA	(United States) Food and Drug Administration
FQN	fluoroquinolone
FSH	follicle-stimulating hormone
GCLP	Good Clinical Laboratory Practice
GD	group dose
HIV	human immunodeficiency virus
hr	hour(s)
HRZE	isoniazid, rifampicin, pyrazinamide, and ethambutol
IB	Investigator's Brochure
ICF	informed consent form
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
INH	isoniazid
IRB	institutional review board
ITT	intent-to-treat
k_a	absorption rate constant
LDMS	Laboratory Data Management System
LPC	Laboratory Processing Chart
MDR-TB	multidrug-resistant tuberculosis
MIC	minimum inhibitory concentration
MITT	modified intent-to-treat
MOP	manual of procedures
MPaZ	moxifloxacin, pretomanid, pyrazinamide
MRHD	maximum recommended human dose
Mtb	*Mycobacterium tuberculosis*
MTT	mean transit time
MUAC	mid-upper arm circumference
NC-	New Combination trial [TB Alliance study naming convention]
NCT	National Clinical Trial Number
NDA	New Drug Application
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NOAEL	no observed adverse effect level
OBR	optimized background regimen
OCSO	(DAIDS) Office of Clinical Site Oversight
OHRP	Office for Human Research Protection
Pa	pretomanid (previously, Pa-824)
PaMZ	pretomanid, moxifloxacin, and pyrazinamide
PCR	polymerase chain reaction
PE	prediction error
PID	participant identification number
PIP	(EMA) Paediatric Investigation Plan
PK	pharmacokinetics

PRO	(DAIDS) Protocol Registration Office
PZA	pyrazinamide
QD	once daily
QTcF	QT interval corrected by Fridericia's formula
RHZ	rifampicin, isoniazid, and pyrazinamide
RIF	rifampicin
RNA	ribonucleic acid
RR-TB	rifampicin-resistant tuberculosis
RSC	(DAIDS) Regulatory Support Center
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCORE	(DAIDS) Site Clinical Operations and Research Essentials Manual
SDMC	Statistical and Data Management Center
SES	(DMC) study enrollment system
SID	study identification number
SMC	(IMPAACT) Study Monitoring Committee
SMQ	Standardized MedDRA Queries
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBA	TB Alliance (previously, Global Alliance for TB Drug Development)
TEAE	treatment emergent adverse event
T_{max}	time of maximal concentration
ULN	upper limit of normal
US	United States
V_d	volume of distribution
VQA	Virology Quality Assurance Program
WB	western blot
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

IMPAACT 2034
Phase I Study of the Pharmacokinetics, Safety, and Acceptability of a Single Dose of Pretomanid Added to an Optimized Background Regimen in Children with Rifampicin-Resistant Tuberculosis

PROTOCOL TEAM ROSTER

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IMPAACT 2034
Phase I Study of the Pharmacokinetics, Safety, and Acceptability of a Single Dose of Pretomanid Added to an Optimized Background Regimen in Children with Rifampicin-Resistant Tuberculosis

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IMPAACT 2034
Phase I Study of the Pharmacokinetics, Safety, and Acceptability of a Single Dose of Pretomanid Added to an Optimized Background Regimen in Children with Rifampicin-Resistant Tuberculosis

SCHEMA

Purpose: To evaluate the pharmacokinetics (PK), safety, tolerability, and acceptability of a single dose of pretomanid, added to an optimized background tuberculosis treatment regimen (OBR), in children with rifampicin-resistant tuberculosis (RR-TB) with or without human immunodeficiency virus (HIV)

Design: Phase I, multi-site, open-label, non-comparative, single-dose study

Study Population: Children less than 18 years of age with RR-TB, assigned female sex at birth, living with or without HIV

Sample Size: Up to 72 to achieve at least 36 evaluable participants overall, with at least nine evaluable in each of the four groups shown in the table below; effort will be made to enroll at least three who weigh less than 8 kg.

Study Drug Pretomanid – 200 mg unscored, oral tablets (adult formulation) and pretomanid 10 mg and 50 mg scored, oral dispersible tablets (pediatric formulation), taken once, as a single dose, by weight as follows:

Group	Weight	Formulation	Pretomanid dose
1: ≥31 kg	≥40 kg	Adult	200 mg
	31-<40 kg	Dispersible pediatric	100 mg
2: 20-<31 kg	20-<31 kg	Dispersible pediatric	100 mg
3: 12-<20 kg	12-<20 kg	Dispersible pediatric	75 mg
4: 4-<12 kg	8-<12 kg	Dispersible pediatric	50 mg
	6-<8 kg	Dispersible pediatric	35 mg
	4-<6 kg	Dispersible pediatric	20 mg

Study Duration: Approximately 25-37 months. Accrual is expected to require approximately 24-36 months (from the date of first enrollment) and enrolled participants will be followed for two weeks.

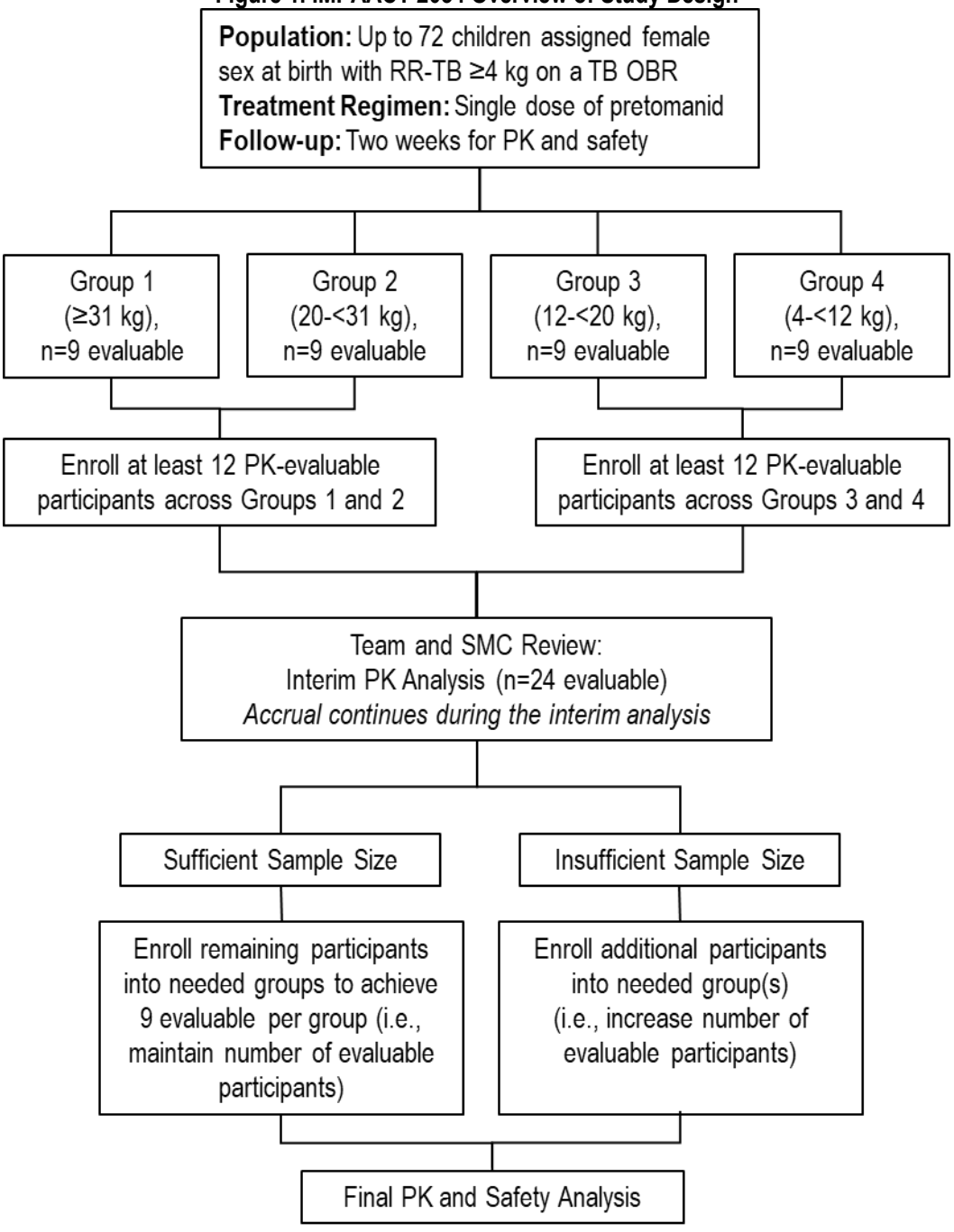
Primary Objectives

- To evaluate the PK of a single dose of pretomanid in children with RR-TB to identify the weight-banded doses of pretomanid to be evaluated in a future multiple-dose study in children

Secondary Objectives

- To evaluate the two-week safety and tolerability of a single dose of pretomanid in children with RR-TB
- To evaluate the acceptability and palatability of a single dose of pretomanid in children with RR-TB

Figure 1. IMPAACT 2034 Overview of Study Design



1 INTRODUCTION

1.1 Background

Globally, an estimated 10 million people fell ill with tuberculosis (TB) in 2019, a number that has been declining very slowly in recent years. While incidence rates and mortality for TB have been falling, it remains one of the world's major causes of illness and death — prompting the World Health Organization (WHO) in 1993 to declare TB to be a global health emergency. While TB is found in every country in the world, it disproportionately affects people in resource-poor settings, particularly those in Asia and Africa. Nevertheless, TB outbreaks still occur in industrialized nations.(1)

Children, defined by the WHO and US Centers for Disease Control and Prevention (CDC) in the context of TB disease as less than 15 years of age, make up 12% of those with TB disease (2). In 2019, 16% of people without human immunodeficiency virus (HIV) who died from TB were children, and 17% of the people living with HIV who died from TB were children. The higher mortality among children compared with their estimated share of cases (12%) suggests disparities and poorer access to diagnosis and treatment.(3)

Rifampicin-resistant tuberculosis (RR-TB), defined as *Mycobacterium tuberculosis (Mtb)* resistant to rifampicin (RIF) continues to pose a significant threat to global public health. There is a large global burden of drug-resistant forms of TB, with an estimated 465,000 incident cases of RR-TB, of which 78% were multidrug-resistant (MDR) TB (defined as *Mtb* resistant to both rifampicin and isoniazid) in 2019.(2) The WHO reports that a global total of 8,986 children with MDR/RR-TB were detected and notified in 2019, less than 10% of the five-year target of 115,000.(2) There are considerable shortfalls in the diagnosis and reporting of childhood tuberculosis. Recent model-based estimates suggested that 25,000 to 32,000 incident cases of MDR-TB occur each year in children globally.(3, 4) RR-TB with additional resistance continues to spread globally, with 20.1% of RR-TB cases being pre-extensively drug-resistant (pre-XDR)-TB (i.e., RR-TB with additional resistance to fluoroquinolones [FQN]).(2)

The political declaration at the first United Nations high-level meeting on TB, held in 2018, included commitments by Member States to setting and meeting global targets for TB treatment. The targets are to diagnose and treat 40 million people with TB in the five-year period from 2018–2022 (including 3.5 million children) and 1.5 million people with drug-resistant TB (including 115,000 children).(2)

The current TB treatment regimens have a lengthy duration of treatment, involve multi-drug therapy, many tolerability issues, and require large commitments of resources and infrastructure. High rates of non-adherence to long and burdensome regimens are common, which often results in chronic infectious cases with drug resistance, and lead to increased mortality for patients and their close contacts. The present TB epidemic and treatment conditions demonstrate the clear need in people with drug-susceptible (DS) or drug-resistant (DR) TB for novel efficacious drugs and drug regimens that will shorten the current treatment duration and be safe and well tolerated. In addition, new TB drugs and regimens should also be affordable, easy to adopt and implement, and suitable for pediatric use and for co-administration with antiretroviral therapy in individuals with concomitant *Mtb* and HIV. Following the declaration of TB as a global emergency by the WHO in 1993, there has been a resurgence of efforts to develop improved TB therapies, and several promising new agents are presently in or approaching clinical evaluation.

However, RR-TB treatment is still being optimized in adults, and crucial aspects of the PK, safety, and efficacy of RR-TB drugs in children are only beginning to be characterized; in some cases, the pediatric development has been significantly delayed. There are several drugs which are in different stages of development but only a few (e.g., bedaquiline, delamanid, clofazimine, rifapentine) have advanced to Phase III clinical trials and are being tested alone or in combination with other anti-TB drugs.(5) Significantly, when bedaquiline was approved by the United States (US) Food and Drug Administration (FDA) in 2012, it was the first new TB drug to have been approved since 1960.

In the eight years that have followed the approval of bedaquiline, one other drug has received FDA approval for the treatment of TB: pretomanid (Pa, or Pa-824). Pretomanid was developed by the TB Alliance (TBA, previously Global Alliance for TB Drug Development) and approved by the FDA on 14 August 2019. Its approval was under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) as part of a combination regimen with bedaquiline and linezolid (BPaL) for people with pulmonary XDR-TB or treatment-intolerant/non-responsive MDR-TB (per WHO definitions preceding January 2021).(6) It also received conditional approval for use in the same patient population by the European Medicines Agency (EMA) on 31 July 2020 and is also being developed for the treatment of DS- and DR-TB.(7)

For the purposes of this protocol, "RR-TB" collectively refers to the following:

- Rifampin mono-resistant TB (RMR-TB, routinely treated as RR-TB), or
- Where additional INH resistance has not been confirmed (i.e., isolated Xpert MTB/RIF-positive resistant cases) and according to case definitions of pediatric TB per WHO definitions (8) and as per local pediatric TB guidelines:
  - MDR-TB (resistance to both RIF and isoniazid [INH]), and
  - Pre-XDR-TB (RR/MDR plus resistance to any FQN), and
  - XDR-TB (RR/MDR plus FQN plus bedaquiline and/or linezolid resistance).

Of note, while pretomanid is approved for treatment of MDR-TB and XDR-TB in adults, this study allows for the enrollment of children with RR-TB. This strategy was discussed with and supported by the Paediatric Committee of the European Medicines Agency (PDCO) and the FDA, primarily by the consideration that RR-TB requires similar clinical management as MDR-TB. In addition, most children who are currently being enrolled in clinical trials of drug-resistant TB and have microbiological confirmation are diagnosed with the WHO-recommended Gene-Xpert test; further sensitivity testing is often unavailable due to the paucibacillary nature of childhood tuberculosis. It would be impractical to perform an array of sensitivity tests in the setting of this study; samples for family or other close contacts may also not be available to allow for additional drug sensitivity analyses; expanding the potential study population to include children with RR-TB will increase the ability to enroll the study while including participants who are treated similarly to those with more extensive drug-resistance.

The study of pretomanid in children with RR-TB is a high priority for research. TBA has developed a Paediatric Investigational Plan (PIP) with the EMA to investigate and define the use of pretomanid in children less than 18 years of age; the study objectives and design, including sample size, weight groups, assessment for formulation palatability and acceptability, and interim analysis requirements correspond with the currently agreed upon plan (EMEA-002115-PIP01-17-M04). In addition, the FDA agreed with the proposed dosing as well as the study follow-up period. In accordance with the PIP, this first-in-children single-dose study will be followed by a multiple (extended) dosing study, once aspects of pretomanid's safety and optimal dosing are better understood. These two studies, in combination, will be critical for defining pretomanid dosing and safety in children.

1.2 Prior Research

Pretomanid has been studied in several contexts. Ongoing clinical trials of the BPaL regimen are underway in countries such as South Africa, Russia, Georgia, and Moldova, as well as operational research programs in Ukraine, Tajikistan, South Africa, Ghana, Laos, etc.(9)

As of December of 2021, pretomanid has been approved in 13 countries – including the Democratic Republic of Congo, Georgia, India, Moldova, Mozambique, South Africa, South Korea, Tajikistan, Turkmenistan, Ukraine, the US, Uzbekistan, and Zimbabwe – and via a centralized procedure in European Economic Area countries. In addition, pretomanid is prequalified by the WHO.

Pretomanid is also being studied in adults for the treatment of TB in four-month and six-month regimens for DS- and DR-TB, respectively, consisting of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (BPaMZ) (NCT03338621) and in the randomized, controlled, Phase II/III trial TB-PRACTECAL, in various combinations with bedaquiline, moxifloxacin, linezolid, and clofazimine (NCT02589782).

The safety of pretomanid has been tested in at least 10 single- and multi-dose, Phase I studies with healthy adult male and female participants, receiving single oral doses of pretomanid ranging from 10 to 1500 mg and multiple oral doses ranging from 200 to 1000 mg/day given for up to 14 days. Pretomanid has also been studied in combination regimens in participants for up to six months (with a few participants whose treatment was extended to nine months per protocol) in Phase II and III studies.(10) See Table 2 for a summary of non-clinical studies and Table 3 for a summary of clinical studies.

1.2.1 Structure and Mechanism of Action

Pretomanid is a nitroimidazooxazine, which kills actively replicating *Mtb* by inhibiting mycolic acid biosynthesis, thereby blocking mycobacterial cell wall production. Under hypoxic conditions, against non-replicating bacteria, pretomanid acts as a respiratory poison following nitric oxide release. All these activities require nitro-reduction of pretomanid within the mycobacterial cell by the deazaflavin-dependent nitro reductase, which is dependent on the reduced form of the cofactor F_{420}. Reduction of F_{420} is accomplished by the F_{420}-dependent glucose-6-phosphate dehydrogenase of *Mtb*, Fgd1.(10)

1.2.2 Nonclinical Studies

Nonclinical studies are summarized below and in Table 2.

Pretomanid has demonstrated in vitro activity against *Mtb* complex, including genetically diverse clinical isolates, and monoresistant and polyresistant/MDR *Mtb*, with the exception of delamanid-resistant *Mtb*, where cross-resistance has been observed for pretomanid against some but not all tested delamanid-resistant strains.(11)

Pretomanid has also demonstrated anti-*Mtb* activity as both a monotherapy and as part of combination regimens in animal models of TB. Regimens with pretomanid, including BPaL, demonstrated efficacy superior to the combination of rifampicin, isoniazid, and pyrazinamide (RHZ). In a study by Li et al., the bactericidal and sterilizing efficacy of BPaMZ; bedaquiline, pretomanid, and moxifloxacin (BPaM); bedaquiline, pretomanid, and pyrazinamide (BPaZ); and

bedaquiline and pretomanid (BPa) were compared to RHZ. At the two- and three-month time points, the combinations BPa and RHZ had similar activities, whereas the BPaM regimen was significantly more active ($p<0.0001$).(12)

Tasneen et al. evaluated the sterilizing activity of bedaquiline, pretomanid, and linezolid as well as the bactericidal activity of the individual drugs, two-drug combinations, and three-drug regimen. All two-drug combinations of bedaquiline, pretomanid, and linezolid had inferior activity (effected smaller colony-forming unit reductions) compared to the activity of the three-drug combination of BPaL at two months ($p<0.01$), confirming that each component drug contributes to the efficacy of the three-drug combination. In addition, the activity of the three-drug combination, BPaL, was superior to that of RHZ after two and three months of treatment ($p<0.001$).(13)

In a series of safety pharmacology studies in rats and monkeys, no central nervous system (CNS), cardiovascular, female reproductive, or respiratory effects were seen at pretomanid exposures consistent with those seen in humans at the maximum recommended human dose (MRHD); effects in all systems were evident at pretomanid exposures that were greater than three-fold higher than those seen with the MRHD. Of note, systemic effects, such as body weight loss, dehydration, and reduced feed consumption, were seen in female rats with repeated, high doses of pretomanid (daily oral doses for two weeks at up to 100 mg/kg/day); however, pretomanid did not appear to directly affect female reproductive function.(14)

No mutagenic or clastogenic effects were detected in both an in vitro bacterial reverse mutation assay and an in vitro mammalian chromosome aberrations assay using a Chinese hamster ovary cell line. Pretomanid showed no clastogenicity in a mouse bone marrow micronucleus assay. In addition, preclinical toxicology studies in rats showed that pretomanid was not teratogenic, and no peri-postnatal effects occurred at doses that did not also produce maternal toxicity in rats.

1.2.2.1 Cataracts

Cataracts were observed in rats treated with pretomanid at high doses of 300 mg/kg/day for 13 weeks or 100 mg/kg/day for 26 weeks. There were no cataracts observed in rats given oral pretomanid at 30 mg/kg/day (approximately twice the human exposure for a 200 mg dose) for 26 weeks.

In a 13-week monkey toxicity study, no cataracts were observed at the end of 13-week dosing, but at the end of the 13-week recovery two animals showed cataracts in the 400/300 mg/kg group. In a subsequent study, cataracts were not observed following 13-week treatment with up to 300 mg/kg/day oral pretomanid or during the 20-week post treatment recovery period. No cataracts were observed in monkeys given oral pretomanid at 100 mg/kg/day for 39 weeks with a 12-week post treatment recovery.

1.2.2.2 Testicular Effects

In nonclinical toxicology studies of pretomanid, testicular degeneration/atrophy has occurred in rats with repeated doses of pretomanid at greater than or equal to 30 mg/kg/day but did not occur in monkeys at any dose level. Four out of 14 rats (29%) exhibited testicular degeneration/atrophy at a dose of 30 mg/kg/day of pretomanid for six months; 100% of rats had testicular degeneration/atrophy at doses higher than 30 mg/kg/day for six months.(15) Testicular effects showed evidence of being partially reversible, albeit very slowly, in rats dosed for seven days, but not in rats dosed for 14 days. As would be expected, there was a dose-related decrease in fertility

in male rats at greater than or equal to 30 mg/kg/day that was associated with decreased sperm numbers and motility. This effect on fertility in male rats was partially reversible. Repeat toxicology studies were conducted in monkeys (0, 50, 150, 300 mg/kg/day for three months; 20-week recovery period) to further explore the male reproductive system effects of pretomanid. In this trial direct testes effects (semen morphology, organ weights, histopathology), or effects on hormones (testosterone, follicle-stimulating hormone [FSH], inhibin B) were not observed at any point during dosing or during the 20-week recovery period.

In two different juvenile rat toxicity studies, testicular toxicity was observed in rat pups administered 100 mg/kg/day for four or eight weeks with four-, eight-, or 16-weeks recovery. The no observed adverse effect level (NOAEL) for juvenile rat testicular toxicity was considered to be 30 mg/kg/day in both studies. In the definitive juvenile study (MPI Research 1408-032), eight-weeks administration of 100 mg/kg/day resulted in germ cell degeneration that affected pachytene spermatocytes and round spermatids with subsequent depletion of elongated spermatids leading to seminiferous tubule degeneration/atrophy. In the same study, four-weeks administration of 100 mg/kg/day did not cause testicular effects but resulted in low sperm motility and concentrations and increased abnormal sperm after four weeks of dosing and four weeks recovery. The NOAEL (30 mg/kg/day) produced maximum concentration (C_{max}) and area under the curve from time zero to 24 hours (AUC_{0-24}) of 6.3 μg/mL and 80 μg*hr/mL, respectively, which is similar to NOAEL exposures in adult rats. In the reproductive function study in juvenile rats (MPI Research, 1408-033), decreased fertility was observed in male rats following eight weeks exposure to pretomanid at 100 mg/kg/day together with adverse effects on sperm parameters, macroscopically small testes and epididymides, and lower weights. There was evidence of partial recovery after 16 weeks. The NOAEL was 30 mg/kg/day.(10)

Pretomanid was not teratogenic, and no peri-postnatal effects occurred at doses that did not also produce maternal toxicity in rats. Pretomanid has phototoxic potential at high dose in rats.

1.2.3 Pharmacokinetics

Based on clinical trials with the marketed formulation of 200 mg tablets, important drivers of PK variability are dosing with or without food and co-administration of medications that induce or inhibit CYP3A4 (cytochrome P450 family 3 subfamily A member 4). Bioavailability in the fasted state was about half that in the fed state, when administered at the clinical dose of 200 mg. Pretomanid is labeled for administration in the fed state. In the presence of RIF and efavirenz, pretomanid average concentration over a dosing interval (C_{avg}) 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 HIV status. The effect of renal or hepatic impairment on the PK of pretomanid is unknown.

1.2.4 Bioavailability Study for Dispersible Tablet

A dispersible-tablet formulation has been developed for pediatric use. Scored tablets in strengths of 10 mg and 50 mg are available. The bioavailability of these dispersible tablets relative to the marketed 200 mg tablets, under both fed and fasted conditions, has been studied in adult healthy volunteers in Study Pa-824-CL-011, which was completed after the US New Drug Application (NDA) filing.(16) The study assessed bioavailability, food effect, and dose dependence of the dispersible formulation intended for pediatric use.

The primary objective of the bioavailability study was to assess the relative bioavailability of a single 200 mg dose of the dispersible formulation intended for pediatric treatment, using a single dose of the 200 mg immediate release formulation as the reference. A total of 48 participants participated in the study and all participants completed the study procedures.

Overall, the investigational product was well-tolerated when administered to healthy participants. There were no serious adverse events (AE) or AEs that led to a participant withdrawal. Under both fed and fasted conditions, the majority of participants evaluated the taste, mouthfeel, and smell of the dispersible pediatric formulation as neither like nor dislike. There were no serious adverse events (SAE) or AEs that led to a participant withdrawal. The most frequently reported treatment emergent adverse event (TEAE) were grade 1 events: constipation (16.7% fed, 4.2% fasted), headache (12.5% fed, 4.2% fasted), and postural orthostatic tachycardia (12.5% fed, 0% fasted).

Under both fed and fasted conditions, pretomanid C_{max} and AUC of the 200 mg treatments (4 x 50 mg dispersible pediatric tablets versus 1 x 200 mg immediate release tablet) were similar.

Under fed conditions, maximum and total pretomanid exposure (C_{max} and AUC) increased in a proportional manner with an increase in pretomanid dispersible pediatric tablet dose over the 10 mg to 200 mg dose range. Under fasted conditions, maximum and total pretomanid exposure (C_{max} and AUC) increased in a less than proportional manner with an increase in pretomanid dispersible pediatric tablet dose over the 10 mg to 200 mg dose range.

Administration of 1 x 200 mg immediate-release tablet with food increased pretomanid C_{max}, $AUC_{0\text{-}tlast}$ (area under the curve from time zero to the last measurable concentration), and $AUC_{0\text{-}\infty}$ (area under the curve from time zero extrapolated to infinite time) by approximately 88%, 68%, and 66%, respectively. Administration of 4 x 50 mg dispersible pediatric tablets with food increased pretomanid C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}\infty}$ by approximately 73%, 88%, and 88%, respectively. Pretomanid C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}\infty}$ were similar after 1 x 50 mg dispersible pediatric tablet administered under fed and fasted conditions. Administration of 1 x 10 mg dispersible pediatric tablets with food reduced pretomanid C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}\infty}$ by approximately 31%, 18%, and 18%, respectively.

1.2.5 Efficacy and Clinical Studies

Clinical studies are summarized below and in Table 3.

At the time of the latest Investigator's Brochure (IB; Version 21, dated 17 December 2021), pretomanid, either alone or as part of a combination regimen, has been used in at least 27 clinical trials sponsored by either TB Alliance or another entity, including more than 2200 participants.

Twenty-four of the trials are considered as the core of the pretomanid developmental program. Two of the core trials, ZeNix and SimpliciTB, are still actively following participants, while another three trials, the hepatic impairment study, renal impairment study, and testicular toxicity study, are still recruiting participants. Detailed safety data from SimpliciTB are not yet available; however, information about deaths is summarized in Table 3. While safety follow-up is still ongoing, analysis of the primary endpoint of the ZeNix trial has been completed. Currently available safety information from ZeNix is incorporated along with safety data from 19 completed core pretomanid trials.

As a single agent, pretomanid showed mycobactericidal activity over 14 days spanning a wide range of doses from 50 to 1200 mg/day: 200, 600, 1000, and 1200 mg/day were tested in Study CL-007 (17); and 50, 100, 150, and 200 mg/day were tested in Study CL-010.(18) The bactericidal activity of pretomanid was similar for all doses tested except 50 mg, which showed less activity than the higher doses.

As treatment of TB requires a combination of multiple drugs, pretomanid was also tested in different combination regimens, measuring bactericidal efficacy over 14 days of treatment in the New Combination 1 (NC-001; NCT01215851) (19) and New Combination 3 (NC-003; NCT01691534) (20) studies, to inform the selection of candidate regimens for later stage clinical development. All pretomanid-containing arms in these two studies showed bactericidal activity. The two best regimens were the combination of pretomanid, moxifloxacin, and pyrazinamide (PaMZ) in NC-001 and BPaZ in NC-003. Both PaMZ and BPaZ showed daily reductions in colony-forming unit counts that were similar to or greater than those in participants administered the standard-of-care four-drug regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE).

PaMZ and BPaZ were further tested over an eight-week treatment period in the NC-002 (NCT01498419) (21) and NC-005. In NC-002, participants with DS-TB were treated with PaMZ, with either 100 or 200 mg/day pretomanid doses. The same combination with 200 mg/day pretomanid was tested in MDR-TB participants. Results indicated that the bactericidal activity of the 200 mg pretomanid regimen was significantly greater than that of HRZE. In contrast, no significant differences were observed between the 100 mg pretomanid regimen and HRZE.

In NC-005, DS-TB participants were treated with BPaZ with bedaquiline administered as either a loading dose (400 mg/day) for 14 days, followed by three times per week at 200 mg/day, or administered consistently at 200 mg/day. Data from this study demonstrated significantly greater bactericidal activity for the BPaZ regimen than for HRZE. The efficacy of the regimen with bedaquiline at 200 mg/day was similar to the efficacy of the regimen with bedaquiline administered as recommended per label (i.e., loading dose and then three times per week). In this study, one study arm of MDR-TB participants was treated with BPaZ (bedaquiline at 200 mg/day) plus moxifloxacin (BPaMZ). The BPaMZ regimen in MDR-TB participants showed the greatest bactericidal activity and the shortest time to culture conversion among all treatment arms, although conclusions for this population were limited by the absence of a randomized control arm.(22)

The Phase III study, NC-006 (NCT02342886) (23), tested the combination PaMZ in DS-TB participants under three different dosing schedules: six months with pretomanid at 200 mg/day, four months with pretomanid at 100 mg/day, or four months with pretomanid at 200 mg/day. An MDR-TB population was also treated with PaMZ for six months (pretomanid at 200 mg/day). This study was placed on partial clinical hold in 2015 due to deaths associated with hepatotoxicity. Following investigations, the partial clinical hold was lifted on 17 August 2016. However, due to delays in enrollment and the promising results of other pretomanid-containing drug regimens, TB Alliance chose not to re-open enrollment when the partial clinical hold was removed, but the already enrolled participants (N=284) were followed to the study endpoints. With this reduced sample size, the study failed to demonstrate non-inferiority in the efficacy of the PaMZ regimens compared with the efficacy of the standard-of-care regimen (HRZE) at six months.

In Nix-TB (NCT02333799) (24), the first clinical trial to evaluate the safety and efficacy of the three-drug, all-oral, six-month BPaL regimen, approximately 90% of participants with highly

resistant TB achieved relapse-free cure status six months after the end of treatment. The study enrolled 71 participants with XDR-TB and 38 participants with treatment-intolerant or treatment-nonresponsive MDR-TB, and the Nix-TB rate of favorable outcomes approximates the rates of treatment success for DS-TB.(25) The study met the pre-specified threshold for success, with the lower bound of the confidence interval (CI) for a favorable outcome far exceeding 50%. Furthermore, the percentage of participants who had a favorable status following this six-month regimen was substantially higher than the rate of favorable outcomes in the reported literature with existing DR-TB regimens lasting 18 months or longer. Nix-TB led to FDA approval of pretomanid in the BPaL regimen combination in August 2019 (6) and EMA approval in July 2020 (7).

Favorable outcome rates were similar for participants with XDR-TB or treatment intolerant/ nonresponsive MDR-TB and across subgroups defined by demographic and baseline disease characteristics and the linezolid treatment regimen (600 mg twice daily [BID], as was originally implemented, or 1200 mg once daily [QD], after a protocol amendment).

Participants on the BPaL regimen converted to culture-negative status quickly, with a median time of less than six weeks. Participants improved clinically; a reduction of TB symptoms and increased body weight accompanied the change in TB status. Most participants remained relapse-free at six months after the end of treatment with preliminary 24-month data indicating that virtually all participants with culture conversion remained relapse free.

The follow-on, randomized, Phase III, ZeNix trial (NCT03086486) enrolled a total of 181 participants 14 years and older with pre-XDR-TB, XDR-TB, or treatment intolerant/ nonresponsive MDR-TB in South Africa, Georgia, Moldova, and Russia. ZeNix expanded on the foundation built by Nix-TB, and randomized participants 1:1:1:1 to one of four arms with varying durations and doses of linezolid for the BPaL regimen; all participants received BDQ 200 mg QD for eight weeks then 100 mg QD for 18 weeks plus pretomanid 200 mg QD for 26 weeks:

- Linezolid 1200 mg QD for 26 weeks (1200L6M)
- Linezolid 1200 mg QD for 9 weeks followed by linezolid placebo for 17 weeks (1200L2M)
- Linezolid 600 mg QD for 26 weeks (600L6M)
- Linezolid 600 mg QD for 9 weeks followed by linezolid placebo for 17 weeks (600L2M)

Each participant was to receive 26 weeks of treatment. If a participant's sputum sample was culture positive between the Week 16 and Week 26 treatment visits and their clinical condition suggested they may have had ongoing active TB, the investigator could consider extending current treatment to 39 weeks.

Of the 181 participants who were randomized in ZeNix, 169 completed treatment. The 181 participants were 67.4% male, and the mean age was 37.1 years. The majority of participants were white (63.5%), and all remaining participants were black or African American (36.5%). The median body mass index (BMI) of all participants was 20.8 kg/m^2 (range 17.1 to 31.0 kg/m^2). The majority of participants had a current TB diagnosis of pre-XDR-TB (47.0%) or XDR-TB (41.4%) at enrollment and reported prior use of at least one TB medication (71.1%). Thirty-six of the 181 participants (19.9%) were living with HIV. The primary efficacy endpoint was the incidence of treatment failure (unfavorable outcome) defined as bacteriologic failure or relapse or clinical failure at six months after the end of therapy. There were 181 participants in the intent-to-treat (ITT) population, 177 of which were included in the modified intent-to-treat (MITT) population because they did not have any late screening failures or any predefined withdrawals/exclusions

during the trial. Four participants in the MITT were un-assessable for the primary efficacy endpoint due to one participant death (violent or accidental), two participants lost to follow-up, and one participant withdrawal.(26)

A high rate of favorable clinical outcomes, similar to Nix-TB, was observed; all treatment groups met the pre-specified threshold for success of the treatment regimen (the lower bound of the 95% CI for a favorable response being greater than 50%), and overall, 89% of all participants in the assessable MITT population had a favorable outcome at 26 weeks (Table 1). All groups (except the 600L2M group) experienced a gradual median decrease in the number of TB symptoms over time. By group, the rate of favorable outcomes was as follows: 93% in 1200L6M, 89% in 1200L2M, 91% in 600L6M, and 84% in 600L2M. The lower bound of the 95% CI ranged from 69.9% in the 600L2M group to 81.3% in the 1200L6M group. The lower bound of the 97.5% CI ranged from 74.0% in the 1200L2M group to 76.4% in the 600L6M group. Sensitivity analyses of the per-protocol and intention-to-treat populations were similar to the primary efficacy analysis.

Adverse events in ZeNix depended on linezolid dose. Participants in the 1200L6M group had higher rates of AEs of peripheral neuropathy and myelosuppression/anemia: 38% and 22% in 1200L6M, 24% and 17% in 1200L2M, 24% and 2% in 600L6M, and 13% and 7% in 600L2M, respectively. Four participants had optic neuropathy that reversed, all in the 1200L6M group. More participants in the 1200L6M group required linezolid dose modification (reduction, interruption, or discontinuation): 51% in 1200L6M, 30% in 1200L2M, 18% in 600L6M, and 18% in 600L2M.(26)

Table 1. Primary Efficacy Analysis of ZeNix Trial (MITT Population)

	n (%)				
	1200L6M (N=45)	**1200L2M (N=46)**	**600L6M (N=45)**	**600L2M (N=45)**	**Total (N=181)**
Unassessable	1	1	1	1	1
Total assessable (MITT)	44	45	44	44	177
Favorable	41 (93.2%)	40 (88.9%)	40 (90.9%)	37 (84.1%)	158 (89.3%)
Unfavorable	3 (6.8%)	5 (11.1%)	4 (9.1%)	7 (15.9%)	19 (10.7%)
95% CI for Favorable	81.3% to 98.6%	75.9% to 96.3%	78.3% to 97.5%	69.9% to 93.4%	83.7% to 93.4%
97.5% CI Favorable	--	74.0% to 96.9%	76.4% to 97.9%	--	--

CI = confidence interval; MITT = modified intent-to-treat; N = total number of participants randomized; n = number of participants in the MITT population; Total assessable = Number of participants in the relevant analysis population (unassessables were not included in the analysis).

Of the 19 participants in the MITT with unfavorable status, four participants withdrew during treatment due to an AE (polyneuropathy, suicide attempt, drug-induced liver injury, and acute alcoholic psychosis), four participants withdrew post-treatment due to confirmed relapse, four participants withdrew due to the participants' decision, four participants withdrew post-treatment due to re-treatment, one participant withdrew due to treatment failure, one participant was withdrawn by the investigator/sponsor due to baseline sensitivity to rifampicin, and one participant was lost to follow-up during the treatment period.

Secondary efficacy endpoints of ZeNix included the time to sputum culture conversion to negative status through the Treatment Period, and other clinical endpoints such as change in weight and BMI and TB symptoms from baseline.

Of the 129 participants who were culture positive at baseline, the median time to culture negative status was four-weeks for the 600L6M group and for both 1200 mg linezolid treatment groups, regardless of total duration of treatment. The 600L2M group had a median time to culture conversion of six weeks. For pretomanid, using the MGIT liquid culture system was determined for *Mtb* isolates at baseline and, when applicable, post Week 16 (the first culture positive for *Mtb* at or after Week 16 was characterized for any participant not responding to therapy, and/or the first positive for *Mtb* during follow-up). Of the 129 baseline isolates tested, two participants had isolates with pretomanid minimum inhibitory concentration (MIC) values greater than 16 μg/mL. Both participants had a favorable outcome. There were three participants who had post-Week 16 isolates with pretomanid MIC values greater than 16 μg/mL (baseline pretomanid MICs were 0.25 μg/mL). Among these, two participants relapsed, and one was withdrawn during treatment.

A Phase IIc study, SimpliciTB, also known as NC-008, is an ongoing partially randomized controlled study which further examines the BPaMZ regimen in both DS and DR participants (NCT03338621).

SimpliciTB is evaluating the efficacy, safety, and tolerability of a novel and potentially shorter duration drug regimen (BPaMZ) for participants with DS and MDR pulmonary TB (specifically MDR-TB and mono-resistance to INH and RIF). The new drug regimen was administered for four months to participants with DS-TB, and for six months to patients with MDR-TB or mono-resistance to RIF or INH. Results in the DS-TB arm will be compared to a control group of the standard six-month drug regimen for DS-TB (HRZE).

As of December 2021, there have been five deaths among participants in SimpliciTB who received at least one dose of pretomanid. Four of these participants (two with DS-TB and two with DR-TB) were randomized to the BPaMZ arm and died during the treatment period; their fatal outcomes were attributed to: embolism, hepatotoxicity, acute kidney injury, sepsis, and severe acute respiratory syndrome and coronavirus disease 2019 (COVID-19). One additional participant (with DS-TB) died due to worsening hypokalemia in the context of cor pulmonale 12 days after the last dose of BPaMZ.

Lastly, the TB-PRACTECAL study is a Phase II/III pragmatic randomized controlled trial run by Médecins Sans Frontières, examining pretomanid in various combinations with bedaquiline, moxifloxacin, linezolid, and clofazimine (NCT02589782). Notably, randomization into TB-PRACTECAL was halted prematurely in March 2021 by the Data Safety and Monitoring Board when it was discovered that the experimental arm had superior outcomes over standard of care.(27)

It is important to note that, while most studies of pretomanid have been only in adults, pretomanid has been studied in some adolescents in a few trials. Adolescents over age 14 years were included in Nix-TB (two 17-year-olds, one 18-year-old, and three 20-year-olds of 109 participants) and ZeNix (four 18-year-olds, two 19-year-olds, and three 20-year-olds of 181 participants), and adolescents over age 15 were included in TB-PRACTECAL but in limited numbers.(24-27)

Table 2. Summary of Non-clinical Studies of Pretomanid

Study	Regimen(s)	Outcome	Result
Li (12)	BPaMZ, BPaM, BPaZ, and BPa vs RHZ (mouse)	Bactericidal and sterilizing activity	At 2- and 3-month time points, combinations BPa and RHZ had similar outcomes, whereas the BPaM regimen was significantly more active ($p<0.0001$)
Tasneen (13)	B, Pa, L	Sterilizing activity of BPaL; bactericidal activity of individual vs 2 vs 3 drugs	All 2-drug combinations of B, Pa, and L had inferior activity compared to the activity of the 3-drug combination of BPaL at 2 months ($p<0.01$), confirming that each component drug contributes to the efficacy of the 3-drug combination
Several studies	Pa (rat; monkey)	Safety pharmacology studies	– No CNS, cardiovascular system, or respiratory effects were seen at Pa exposures consistent with those seen in humans at the MRHD – Effects were evident at Pa exposures greater than three times the MRHD
	Pa (Chinese hamster; mouse)	Mutagenic or clastogenic effects	– No mutagenic effects were detected – Pa showed no clastogenicity
	Pa (rat)	Cataracts	– Cataracts observed in rats treated with Pa at high doses – No cataracts observed in rats given oral Pa at approximately twice the human exposure
Several studies	Pa (monkey)	Cataracts	– In 13-week study, no cataracts were observed at the end of 13-week dosing, but at the end of the 13-week recovery two animals showed cataracts in the 400/300 mg/kg group
	Pa (monkey)	Cataracts	– No cataracts observed following 13-week treatment with up to 300 mg/kg/day oral Pa or during 20-week post treatment recovery period – No cataracts were observed in monkeys given oral Pa at 100 mg/kg/day for 39 weeks with a 12-week post treatment recovery
Personal comm. (15)	Pa (rat; monkey)	Non-clinical toxicology studies – testicular degeneration/ atrophy	– Testicular degeneration/atrophy occurred with repeated doses ≥30 mg/kg/day in rats but not in monkeys at any dose level – 4/14 rats (29%) exhibited testicular degeneration/atrophy at a dose of 30 mg/kg/day for 6 months; 100% of rats had testicular degeneration/atrophy at doses higher than 30 mg/kg/day for 6 months – Testicular effects showed evidence of slow partial reversibility in rats dosed for 7 days, but not if dosed for 14 days – There was a partially reversible dose-related decrease in fertility in male rats at ≥30 mg/kg/day associated with decreased sperm numbers and motility
	Pa (monkey)	Non-clinical toxicology studies (male reproductive effects)	– Repeat toxicology studies conducted (0, 50, 150, 300 mg/kg/day for 3 months; 20-week recovery period) – Direct testes effects (semen morphology, organ weights, histopathology), or effects on hormones (testosterone, FSH, inhibin B) were not observed at any point during dosing or during the 20-week recovery period
	Pa (rats)	Non-clinical toxicology studies (teratogenicity; phototoxicity)	– Pa was not teratogenic, and no peri-postnatal effects occurred at doses that did not also produce maternal toxicity in rats – Pa has phototoxic potential at high dose in rats

Table 3. Summary of Phase II and III Clinical Studies of Pretomanid in Adults with MDR-TB or XDR-TB

Study (N)	Phase	Regimen (Population)	Outcome	Result
NC-002 (N=207)	II	PaMZ for 8 wks then standard of care (DS-TB 100 or 200mg/day Pa; MDR-TB 200mg/day Pa)	Change in sputum colony forming units at 8 wks of treatment (bactericidal activity; solid medium)	• Bactericidal activity of the 200mg Pa regimen significantly greater than that of HRZE • No significant differences between the 100mg Pa regimen and HRZE
NC-005 (N=240)	II	BPaZ and BPaMZ for 8 wks then standard of care (DS-TB; MDR-TB)	Rate of change in time to sputum culture positivity over 8 wks (bactericidal activity; MGIT)	• BPaZ had significantly greater bactericidal activity than HRZE • Regimen with BDQ 200mg/day equivalent in efficacy to loading dose regimen • BPaMZ regimen in MDR-TB participants had greatest bactericidal activity and shortest time to culture conversion • No randomized control arm
NC-006, STAND (N=284)	III	PaMZ for 6 months[1] (DS-TB; MDR-TB) PaMZ in DS-TB participants under 3 dosing schedules: 6 mths Pa at 200mg/day, 4 mths Pa at 100mg/day, or 4 mths Pa at 200mg/day. MDR-TB participants also treated with PaMZ for 6 mths (Pa at 200mg/day)	Incidence of combined bacteriologic failure or relapse at 12 months from start of therapy	• Study placed on partial clinical hold in 2015 due to deaths associated with hepatotoxicity (later lifted) • TB Alliance chose not to re-open enrollment but follow all already enrolled participants (N=284) to the study endpoints • With the reduced sample size, study failed to demonstrate non-inferiority of PaMZ regimens compared HRZE at six months
NC-008, SimpliciTB (N=450)	II	BPaMZ for 6 mth[1] (DS-TB; MDR-TB)	Time to culture conversion over 8 wks	• Full results not yet available (results available in Q2 2022) • Five deaths in BPaMZ arm
Nix-TB (N=109; n=71 XDR-TB and n=38 TI/NR MDR-TB)	III	BPaL for 6 mth[1] (XDR-TB; TI/NR[2] MDR-TB)	Relapse-free cure at 12 mths	• 90% of participants achieved relapse-free cure status 6 mth after end of treatment (approximates the rates of treatment success for DS-TB) • Met the pre-specified threshold for success • Led to FDA approval of Pa in the BPaL regimen combination in August 2019 and EMA approval in July 2020
NC-007, ZeNix (N=181)	III	BPaL for 6 mth[1] (XDR-TB; TI/NR[2] MDR-TB)	Incidence of bacteriologic failure or relapse/clinical failure through 78 wks	• High rate of favorable clinical outcomes: 93% in 1200L6M, 89% in 1200L2M, 91% in 600L6M, and 84% in 600L2M • 1200L6M arm had higher rates of adverse events of peripheral neuropathy and myelosuppression/ anemia

mth=months; wk=weeks; [1](26 weeks); [2]Treatment Intolerant/Non-responsive; [3]Bedaquiline was administered either with a loading dose (400 mg/day) for 14 days, followed by 3 times per week at 200 mg/day, or administered at 200 mg/day for 8 weeks, and then 100mg/day for 18 weeks.

1.2.6 Safety

All single- or multiple-dose Phase I studies of pretomanid have been conducted in adult healthy volunteers. The most frequently reported preferred terms of TEAE in the Phase I pretomanid pooling group were headache (31.5%) and nausea (11.8%). In the control group, headache was reported as 22.9%.(10)

The adverse drug reactions (ADR) were identified, at the time of NDA filing, from the pooled safety database of reported AEs in the Phase I studies, where a placebo arm was available, and Phase II/III clinical studies, where a standard of care arm was available, with data from other non-controlled studies, including results from exposure/response modeling of Nix-TB, as supporting evidence. The ADR list has not yet updated since then. ADRs for pretomanid include mild to moderate (grade 1 to grade 2) nausea and vomiting, grade 1 to grade 2 rash, and increased transaminases.

1.2.6.1 Creatinine and Hepatic Enzymes

A study of the effects of repeat doses of pretomanid in healthy volunteers showed reversible elevations in serum creatinine. It was determined that the drug does not adversely affect glomerular filtration rate, effective renal plasma flow, or filtration fraction, and therefore the observed elevations in serum creatinine are considered clinically benign.(10)

Hepatic enzyme increases have been seen in participants treated with pretomanid in combination with various other medications during the clinical development program. It is difficult to assign specific causality to any one drug within a regimen.

1.2.6.2 QT Interval

Based on the pre-clinical data, results of a thorough QT study, and clinical data on pretomanid, QT prolongation is not considered to be an ADR caused by pretomanid.(10) For pretomanid alone, at 3.2 ug/mL, a typical steady-state C_{max}, or typical maximal exposures expected in clinical practice when pretomanid 200 mg is administered with food as a component of the BPaL regimen, the estimated value of QTc difference from placebo (ΔΔQTcN) was 5.1 ms, with an upper limit of the 90% confidence interval of 6.2 ms.(28) However, as pretomanid is always applied in a regimen where the companion drug(s) (for example, bedaquiline) may be associated with electrocardiogram (ECG) interval prolongation and cardiac rhythm disturbance AEs, ECG data continue to be closely monitored. This is also reflected on the pretomanid US label and the EMA Summary of Product Characteristics, given pretomanid is approved in the context of the BPaL regimen.

1.2.6.3 Effect on Pancreas

Pancreatitis was an AE of interest, based on findings in bedaquiline nonclinical toxicology studies.(28) Increased amylase, increased lipase, and pancreatitis are also known to be associated with HIV and the drugs used to treat it.(29-31) In the Nix-TB study, where half of the participants were living with HIV and received antiretrovirals (ARV), 23 participants (21.1%) reported at least one TEAE in the modified Standardized MedDRA Queries (SMQ) for acute pancreatitis, with the most frequently reported preferred terms being “amylase increased,” “hyperamylasemia,” and “lipase increase.” The incidence of events in this SMQ was greater in the subgroup living with HIV (26.8%) than that in the subgroup living without HIV (15.1%) within Nix-TB. Acute pancreatitis was a contributing cause of death in two (1.8%) participants;

both participants had hemorrhagic pancreatitis confirmed at autopsy. Their risk factors for pancreatitis included HIV/ARV (two participants) and alcohol use (one participant). One additional participant, living with HIV, with no history of alcohol use had a maximum lipase level of 129 U/L (normal range 13-60 U/L) on BPaL and was asymptomatic and diagnosed on abdominal ultrasound as having pancreatitis. This participant did not appear to have acute pancreatitis clinically. BPaL was interrupted for approximately 20 days and lipase levels returned to normal ranges following re-challenge with BPaL. Among participants with normal lipase levels at baseline, elevations post-baseline were observed in 18 (16.5%) participants, and most of the participants had maximum levels less than or equal to two times the upper limit of normal (≤2 x ULN). Four (3.7%) participants had a maximum post-baseline elevation in lipase >2-5 x ULN on BPaL treatment and one (0.9%) participant who had a mild elevation in lipase at baseline had elevated lipase levels >5-10 x ULN post-baseline.(32)

1.2.6.4 Evaluation of Non-Clinical Cataract Toxicities

In follow-up of the non-clinical findings of cataract toxicities, assessment by slit-lamp examination with Age-Related Eye Disease Study 2 (AREDS2) scoring of lens opacities in three anatomic regions of the lens were implemented in all studies with treatment duration greater than 14 days.(10) Both increases and decreases in AREDS2 of ≥1 were observed in a small percentage of eyes, suggesting normal variation in the rater's interpretation and/or age-related changes, with no clinically meaningful effect of pretomanid on cataract formation in Nix-TB, NC-002, NC-005, and NC-006. Also, when the safety database was searched for adverse events (with SMQ lens disorders) at the time of NDA filing, no clear clinical signal or concern was identified. Subsequently, on 6 July 2020, the US FDA concluded that the clinical data submitted in the NDA for pretomanid showed no clinically meaningful effect of pretomanid on the potential for cataract formation at the doses and durations studied. The FDA also agreed that TB Alliance could discontinue slit-lamp examinations for all future sponsored clinical trials for pretomanid.

1.2.6.5 Efficacy Studies in Adults

The studies ZeNix (BPaL) and SimpliciTB (BPaMZ) are ongoing, and thus the safety data are not yet fully available. Both studies have completed enrollment as of 2 March 2020, and the last data and safety monitoring committee meetings held for both studies recommended to continue the studies unmodified.

As of 26 May 2020, 149 participants with DR-TB were enrolled in the SimpliciTB study and received at least one dose of the study drug regimen. Seventeen participants reported at least one SAE, and six of these participants had SAEs of hepatobiliary disorders or elevated/abnormal hepatic enzymes. Of these, there has been one death in a participant who had acute renal failure and sepsis, and another death in a participant who died of COVID-19 in the DR BPaMZ arm.

1.2.6.6 Evaluation of Non-Clinical Testicular Effects

In follow-up to the non-clinical findings of testicular toxicity, males in four trials, NC-002 (MPaZ), NC-005 (BPaZ), NC-006 (PaMZ), and NC-008 (BPaMZ), were evaluated by plasma sampling for the reproductive hormones (luteinizing hormone, FSH, inhibin-B and testosterone; note: luteinizing hormone was not measured in NC-005) at baseline and at the end of the treatment period. DS/DR-TB participants in those four trials received two to six months of regimens containing 100 or 200 mg pretomanid, or HRZE. The pooled analysis indicated that treatment regimens with either 100 or 200 mg/day pretomanid administered for up to six months and standard of care (HRZE) similarly improved male hypogonadism present at baseline in DS-

and DR-TB participants in four studies, indicating a lack of adverse effects of pretomanid on male reproductive function.(33) Table 4 shows exemplative findings from NC-002.

Table 4. FSH Levels at Baseline and End of Therapy in NC-002

Group (N)	Mean Baseline FSH	Mean End of Therapy/Day 56 FSH
M-Pa_{100}-Z (21)	9.03 U/L	8.34 U/L
M-Pa_{200}-Z (19)	6.53 U/L	6.06 U/L
HRZE* (23)	7.39 U/L	6.71 U/L
*Dose: 150 mg RIF, 75 mg INH, 400 mg pyrazinamide (PZA), 275 mg ethambutol (EMB)		

The clinical data consistently showing no effect of pretomanid on reproductive hormone levels in males are reassuring and provide the rationale for undertaking a single-dose study in children, for which the risk of testicular toxicity is expected to be low. A testicular toxicity study, Pa-824-CL-012 (NCT04179500), in adult humans is currently being conducted as a post-marketing commitment and will be completed before a multi-dose evaluation of pretomanid in children is undertaken.

In addition, a paternity study was conducted to collect additional data on male reproductive function during or after treatment with a regimen containing pretomanid. Male participants from four studies (NC-006/STAND, Nix-TB, ZeNix, and SimpliciTB) were contacted and asked to consent to complete a questionnaire about partner births that occurred while receiving pretomanid or after completing a pretomanid-containing regimen. The total number of potential participants was 451; as of March 2022, a total of 322 male participants (71% of the potential total) consented to complete the survey and 45 children were fathered. This observational study was completed in 2022.

1.3 Rationale

1.3.1 Overall Study Rationale

The treatment of RR-TB in children could be dramatically improved with new, effective, and safer oral drugs, with the goal of shortening RR-TB therapy, limiting toxic injectables, and reducing adverse effects and poor tolerability. The emergence of XDR-TB requires a wider choice of medications.

This critical study forms the foundation of developing just such a medication for children with RR-TB; participants will be evaluated with a single dose of the novel TB drug, pretomanid, in children being treated for RR-TB disease, with an optimized background regimen, with the goals of collecting safety and PK data in children given a single dose of pretomanid. Doses selected for this study have been chosen because, based on modeling, they are expected to yield exposures, as measured by $AUC_{0-\infty}$ after a single dose, close to 50.9 µg*hr/mL, the median value of steady-state AUC_{0-24} observed in the Nix-TB study. See Section 10.3 for full details. Importantly, the PK data collected in this first-in-children, single-dose study is expected to adequately inform the pharmacometric modeling and establish a starting dose for a future multi-dose, dose-confirming study of pretomanid in children with RR-TB.

1.3.2 Rationale for Selected Study Population

While this protocol was initially designed to include children regardless of sex at birth, the FDA subsequently concluded that there may be greater than minimal risk of testicular toxicity from a single dose of pretomanid based on preclinical data. Therefore, only participants assigned female sex at birth will be enrolled in IMPAACT 2034.

As sex was not a significant covariate in determining PK in adult studies (34) and the same is expected to be true in children and adolescents, limiting enrollment and evaluation to participants assigned female sex at birth is not anticipated to have an impact on the strength or validity of the results from this study, when used to inform subsequent studies of pretomanid. Once additional safety results from the testicular toxicity study (Pa-824-CL-012, NCT04179500) are available, it is expected that enrollment will not be limited by sex at birth in the subsequent multi-dose study.

For this study and for subsequent studies of pretomanid in children, it is important to note the differences in potential risk-benefit ratios for the study populations. Notably, in IMPAACT 2034, participants may experience no direct benefit (see Section 13.4); if participants assigned male sex at birth were included in the study population, their potential risk may outweigh the potential benefit, until further data are available. However, it is anticipated that the potential benefits may balance the potential risks more in subsequent multi-dose studies including pretomanid, as pretomanid will be an active agent in participants' RR-TB combination treatment regimen; inclusion of pretomanid in the combination regimen may also allow for avoidance of other drugs with documented toxicities. In these future, multi-dose studies, the risk-benefit considerations would likely favor enrolling children regardless of sex at birth (male, female, intersex, etc.).

Children living with HIV are eligible for the study as long as they are not taking prohibited ARVs. No minimum number of children living with HIV are required in the study as there has not been a demonstrated effect of HIV on pretomanid pharmacokinetics to date, and the study is not powered to identify any effect of HIV. Additionally, as the proportion of children with RR-TB who are living with HIV is relatively small (8), it will be a challenge to efficiently enroll this subgroup, so minimum enrollment requirements may unnecessarily delay study accrual. Notably, no clinically significant differences in the PK of pretomanid were observed in adult studies based on HIV status.(34)

1.4 Hypotheses

The hypotheses of this study are:

- The PK characterization in children after receipt of a single dose of pretomanid will inform selection of weight-banded dosing that will inform future multi-dose strategies in children.
- Single dose of pretomanid oral and dispersible tablets will be described as safe and well-tolerated in children with RR-TB less than 18 years of age.

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to:

2.1.1 Evaluate the pharmacokinetics of a single dose of pretomanid in children with RR-TB to identify the weight-banded doses of pretomanid to be evaluated in a future multiple dosing study in children

2.2 Secondary Objectives

The secondary objectives of this study are to:

2.2.1 Evaluate the two-week safety and tolerability of a single dose of pretomanid in children with RR-TB

2.2.2 Evaluate the acceptability and palatability of a single dose of pretomanid in children with RR-TB

2.3 Exploratory Objectives

The exploratory objective of this study is to:

2.3.1 Evaluate the contribution of dose, demographic and baseline characteristics, and HIV status and/or its treatment to the variability in pretomanid drug disposition, using population PK modeling

3 STUDY DESIGN

This is a Phase I, multi-site, open-label, non-comparative study of the PK, safety, tolerability, and acceptability of a single-dose of pretomanid added to an OBR in infants, children, and adolescents with RR-TB. The term children is used within the protocol to indicate the total age range from infants through adolescents; as noted in Section 1.3, enrollment will be limited to children assigned female sex at birth. Refer to Figure 1 for an overview of the study design and to Section 4 for the study eligibility criteria and a description of the study recruitment, screening, and enrollment process. Participants are expected to be enrolled at study sites in Brazil, India, South Africa, Tanzania, and Thailand.

Participants will receive a single dose of pretomanid on the day of study entry; refer to Section 5 for more detailed information on study drug considerations. No additional doses of pretomanid will be administered; participants will continue their OBR. Intensive PK sampling will be performed on the day of study entry and over the course of the next 48 hours. Participants will then complete a final study visit approximately two weeks after study entry. Refer to Section 6 and the Schedule of Evaluations in Appendix I for procedures to be performed at each study visit.

As specified in the PIP, participants will be assigned to one of the four groups by weight at entry. Up to 72 participants will be enrolled in the four groups shown in Table 5 to achieve at least nine evaluable participants in each group; within Group 4, effort will be made to enroll at least three

evaluable participants who weigh less than 8 kg. To be considered evaluable, participants must be both PK-evaluable and safety-evaluable, which are defined as follows:

- PK-evaluable: Participants will be considered PK-evaluable if they receive (ingest) the single dose of pretomanid being evaluated and undergo intensive PK sampling with at least five of the six planned intensive PK samples collected, including the 48-hour sample.
- Safety-evaluable: Participants will be considered safety-evaluable if they receive (ingest) the single dose of pretomanid being evaluated and complete the Week 2 visit.

The Protocol Team will closely monitor the number of participants confirmed to meet the above-listed definitions. Participants who are not confirmed as evaluable will not be counted toward the study accrual quotas but will be retained on-study and included in primary and secondary analyses, unless otherwise specified in Sections 9 and 10.

The study sample size and accrual quotas have been specified based on information currently available from PK modeling. As modeling to date has been based only on adult data, and as specified in the PIP, an interim analysis will be performed to confirm the adequacy of the study sample size and accrual quotas. Refer to Section 10.4 for a further description of the interim analysis, which will be performed following enrollment of at least 12 PK-evaluable participants across groups 1 and 2 and at least 12 PK-evaluable participants across groups 3 and 4 (i.e., at least 24 PK-evaluable participants total). The results of this analysis, as well as all available PK and safety data, will be reviewed by the Clinical Management Committee (CMC) and the IMPAACT Study Monitoring Committee (SMC) to determine whether the current sample size of nine evaluable participants per group is sufficient or if the sample size should be increased for any of the four groups to achieve the study objectives. Accrual into the study will remain open while the interim analysis is being completed and data are being reviewed by the CMC and SMC. However, the number of participants enrolled will not exceed the targeted number evaluable for each group.

Final primary and secondary analyses will be performed after all participants have completed follow-up through the Week 2 visit. Refer to Sections 9 and 10 for more detailed information on data analysis and statistical considerations and pharmacology considerations.

4 STUDY POPULATION

This study will be conducted among at least 36 and up to 72 children with RR-TB who will be selected for the study according to the criteria in Sections 4.1-4.3 and the guidelines in Section 4.4. The study-specific approach to recruitment, screening, and enrollment is described in Section 4.5. Considerations related to participant retention and withdrawal or termination from the study are provided in Sections 4.6 and 4.7, respectively.

Note: Several of the eligibility criteria specified in Sections 4.1-4.3 refer to eligibility determination based on participant/parent/guardian report and available medical records. For these criteria, it is expected that relevant information will be requested from the participant/ parent/guardian and that available medical records will be reviewed for information relevant to these criteria. Unless otherwise specified, both participant/parent/guardian report and medical records are not required. For example, it is not expected that a participant/parent/guardian will be able to recall all information recorded in medical records, and medical records are not required to substantiate participant/parent/guardian report. However, all available medical records must be

reviewed and the totality of information from both sources must be considered when making eligibility determinations.

4.1 Inclusion Criteria

Potential participants must meet all of the criteria specified below to be included in this study; in these criteria, "at entry" is used to refer to the day of enrollment in this study, i.e., at the Day 0 (Entry) Visit:

4.1.1 *If not of legal age or circumstance to provide independent informed consent as determined by site standard operating procedures (SOPs) and consistent with institutional review board/ethics committee (IRB/EC) policies and procedures:* Parent/legal guardian is willing and able to provide written informed consent for potential participant's study participation; in addition, when applicable per IRB/EC policies and procedures, potential participant is willing and able to provide written assent for study participation.

If of legal age or circumstance to provide independent informed consent as determined by site SOPs and consistent with IRB/EC policies and procedures: Potential participant is willing and able to provide written informed consent for study participation.

Note: All sites must follow all applicable IRB/EC policies and procedures.

4.1.2 Assigned female sex at birth, as determined by the site investigator based on participant and parent/guardian report and available medical records

4.1.3 Age less than 18 years of age at entry

4.1.4 Weight greater than or equal to 4 kg at entry

4.1.5 Has confirmed or probable intrathoracic (pulmonary) RR-TB and/or any form of extrathoracic (extrapulmonary) RR-TB *(other than TB meningitis, which is exclusionary per criterion 4.2.1)*

4.1.5.1 Confirmed intrathoracic (pulmonary) RR-TB, based on chest radiograph and/or symptoms consistent with TB, and/or any forms of extrathoracic TB, with all of the following, as determined by the site investigator based on medical records:

- Microbiological confirmation of *M. tuberculosis* from any clinical specimen by either culture or molecular methods
- Rifampicin resistance demonstrated by genotypic (molecular) or phenotypic methods
- Documented clinical decision to treat for RR-TB

Note: In the case of discrepant genotypic and phenotypic test results (i.e., rifampicin-susceptible by one method and rifampicin-resistant by another), this criterion will be considered to have been met if at least one rifampicin-resistant result is available and the participant is assessed as having RR-TB by the non-study care provider when study staff evaluate the participant for eligibility.

4.1.5.2 Probable intrathoracic (pulmonary) RR-TB, based on chest radiograph and/or symptoms consistent with TB, and/or any form of extrathoracic TB, with both of the following, as determined by the site investigator based on medical records:

- Documented exposure to a source case with bacteriologically-confirmed intrathoracic rifampicin-resistant TB
- Documented clinical decision to treat for RR-TB

Note: Full resistance profiles may be obtained after study entry.

4.1.6 Initiated an appropriate TB OBR treatment regimen as per routine treatment decision, at least two weeks prior to entry, as determined by the site investigator based on medical records, and is tolerating the regimen well at entry, in the opinion of the site investigator

Note: See exclusion criterion 4.2.2 for exclusionary TB medications.

4.1.7 Has normal, grade 1, or grade 2 results for all of the following at screening (i.e., from specimens collected within 28 days prior to entry), based on grading per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table; refer to Section 7.3.3 for guidance on severity grading):

4.1.7.1 Creatinine
4.1.7.2 Platelets
4.1.7.3 Absolute neutrophil count
4.1.7.4 Hemoglobin
4.1.7.5 Estimated glomerular filtration rate (eGFR; bedside Schwartz formula)

Note: Laboratory tests may be repeated during the study screening period (i.e., within 28 days prior to entry), with the latest results used for eligibility determination.

4.1.8 Has normal or grade 1 results for all of the following at screening (i.e., from specimens collected within 28 days prior to entry), based on grading per the DAIDS AE Grading Table (refer to Section 7.3.3 for guidance on severity grading):

4.1.8.1 Alanine aminotransferase (ALT)
4.1.8.2 Lipase
4.1.8.3 Total bilirubin

Note: Laboratory tests may be repeated during the study screening period (i.e., within 28 days prior to entry), with the latest results used for eligibility determination.

4.1.9 Has a normal QT interval corrected by Fridericia's formula (QTcF) (mean interval value less than 450 milliseconds, on ECG performed in triplicate) at screening

Note: The mean QTcF value obtained from the centralized ECG reading must be used for eligibility determination.

4.1.10 Has a Karnofsky score greater than or equal to 50% for participants 16 years of age and older or Lansky play score greater than or equal to 50% for participants less than 16 years of age, at screening

4.1.11 Does not have severe acute malnutrition, defined below, and has no presence of nutritional edema, based on physical examination, at screening

Severe acute malnutrition is defined as any of the following:

- For participants 5 years of age and younger: weight-for-height z-score less than -3, according to WHO growth standards
- For participants 6 months to 5 years of age: mid-upper arm circumference (MUAC) less than 115 mm
- For participants older than 5 years of age: BMI z-score less than -3, according to WHO growth standards

Note: Children who are stunted may be enrolled.

4.1.12 HIV status determined based on testing methods meeting the requirements specified in Section 4.3

4.1.13 For participants living with HIV, has been taking a stable ARV regimen for at least two consecutive weeks at entry, as determined by the site investigator based on participant and parent/guardian report and available medical records

Note: Dose and formulation changes (e.g., for growth) within the two weeks prior to entry are permitted. See exclusion criterion 4.2.2.3 for exclusionary ARVs.

4.1.14 *For participants who have reached menarche or who are engaging in sexual activity (self-reported)*: not pregnant based on testing performed during the study screening period (i.e., within 28 days prior to entry)

4.1.15 *For participants who are engaging in sexual activity (self-reported):* agrees to use at least one effective, medically accepted birth control method while on study, based on participant and parent/guardian report at entry

4.1.16 Expected to be available for two weeks of study participation, based on participant and parent/guardian report at entry

4.2 Exclusion Criteria

Potential participants must be excluded from the study if any of the conditions specified below are identified during the screening period. The screening period begins when informed consent is obtained and ends immediately prior to enrollment. For criteria involving a potential participant's medical history, it is expected that each exclusionary condition will be assessed at screening and subsequently reviewed and confirmed on the Day 0 (Entry) Visit, prior to enrollment.

4.2.1 Has tuberculosis meningitis Stage 2 or 3, as determined by the site investigator based on medical records

4.2.2 Receipt of any of the following, within 14 days prior to entry, as determined by the site investigator based on participant/parent/guardian report and available medical records

4.2.2.1 Rifamycins
4.2.2.2 Any prohibited medication (see Section 5.8)
4.2.2.3 *For participants living with HIV:* ritonavir-boosted protease inhibitors (e.g., ritonavir-boosted lopinavir, ritonavir-boosted darunavir), atazanavir, nevirapine etravirine, efavirenz, or cobicistat

4.2.3 Receipt of any investigational agent or device within 28 days prior to entry, as determined by the site investigator based on participant/parent/guardian report and available medical records

Note: Co-enrollment in COVID-19 vaccine studies and receipt of a COVID-19 vaccine under emergency use authorization (or local equivalent) is allowed, with prior approval from the CMC.

Note: Any co-enrollment must be approved as noted in Section 4.4.

4.2.4 Has any of the following as determined by the site investigator based on participant/parent/guardian report and available medical records

4.2.4.1 Clinical evidence of acute hepatitis A, B, C, or chronic hepatitis B or C
4.2.4.2 Significant cardiac arrhythmia that requires medication or increases the risk for Torsade de Pointes
4.2.4.3 Known allergy or hypersensitivity to pretomanid or other nitroimidazole compounds
4.2.4.4 Known porphyria

4.2.5 Currently breastfeeding an infant at entry, as determined by the site investigator based on participant/parent/guardian report

4.2.6 Exposed to pretomanid through breast milk within seven days prior to entry (i.e., mother receiving pretomanid and breastfeeding a potential participant), as determined by the site investigator based on parent/guardian report

4.2.7 Has any documented or suspected clinically significant medical condition or any other condition that, in the opinion of the site investigator, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving study objectives

4.3 Determination of HIV Status

HIV status must be determined prior to study entry as specified below. Initial steps will be based on whether a potential participant is presumed to be living with or without HIV based on available medical history information. HIV testing will then be performed as needed to determine each participant's status as specified in the remainder of this section.

4.3.1 Presumed Living without HIV

For potential participants initially presumed by study staff to be living **without** HIV based on available medical history information and/or participant/guardian report, HIV testing must be performed in the study site's designated testing laboratory during the study screening period per Sample #1 requirements in Section 4.3.3.

- Potential participants with negative results will be considered living without HIV at entry.
- Potential participants with positive results should be referred to non-study sources of HIV care and treatment as soon as possible. These potential participants may be considered for entry into the study as participants living with HIV if HIV infection is confirmed per the requirements in Sections 4.3.2 and 4.3.3.

4.3.2 Presumed Living with HIV

For potential participants initially presumed by study staff to be living **with** HIV based on available medical history, HIV status must be confirmed based on test results from two samples collected from two separate blood collection tubes per Sample #1 and Sample #2 requirements in Section 4.3.3. Test results may be obtained from medical records or from testing performed during the study screening period:

- For results obtained from medical records, adequate source documentation, including the date of specimen collection, date of testing or date of test result, name of test/assay performed, and test result, must be available in study records prior to study entry. Requirements related to laboratory operations (e.g., Good Clinical Laboratory Practice [GCLP] or Virology Quality Assurance Program [VQA]) and related to regulatory authority approvals (e.g., FDA) do not apply to results obtained from medical records.
- If adequate source documentation is not available, Sample #1 and/or Sample #2 should be collected during the study screening period and tested in the site's designated testing laboratory. If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to GCLP guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in the study site's VQA-certified laboratory.

Potential participants with positive results from Sample #1 and Sample #2 meeting the requirements listed above will be considered living with HIV at entry. Potential participants with positive results should be referred to non-study sources of HIV care and treatment as needed.

4.3.3 HIV Testing Requirements

All study-specific samples tested to determine HIV status must be whole blood, serum, or plasma. HIV testing methods and algorithms must be approved for each site by the IMPAACT Laboratory Center (for NIAID-funded sites) or Westat (for NICHD-funded sites). Testing methods should be FDA-approved, if available.

In the event of discordant results that the second test does not confirm an initial positive result, the CMC should be consulted for guidance on next steps to clarify the participant's HIV status. Pending confirmatory testing, prophylaxis and treatment should be managed consistent with local standards of care.

Sample #1 may be tested using any of the following:

For participants two years of age and older with no exposure to breast milk in the past 28 days:

- Rapid antibody-based test(s) (combination antigen-antibody-based rapid tests may be used):
  - *For potential participants presumed to be living without HIV:* One FDA-approved rapid antibody-based test (i.e., it is not necessary to perform two rapid tests)
  - *For potential participants presumed to be living with HIV:* Two rapid antibody-based tests from different manufacturers or based on different principles and epitopes
- One enzyme immunoassay (EIA) or Western blot (WB) or immunofluorescence assay or chemiluminescence assay
- One HIV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR)
- One quantitative HIV ribonucleic acid (RNA) PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

For participants less than two years of age or participants two years of age and older with any exposure to breast milk in the past 28 days:

- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

Note: If the participant's mother or the participant is receiving antiretroviral drugs, an HIV DNA assay may be more sensitive.

Sample #2 may be tested using any of the following:

For participants two years of age and older with no exposure to breast milk in the past 28 days:

- Rapid antibody-based test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved, and the third rapid test must be from a third manufacturer or based on a third principle or epitope. Combination antigen-antibody-based rapid tests may be used.
- One EIA or WB or immunofluorescence assay or chemiluminescence assay
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

For participants less than two years of age or with any exposure to breast milk in the past 28 days:

- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

Note: If the participant's mother or the participant is receiving antiretroviral drugs, an HIV DNA assay may be more sensitive.

4.4 Co-Enrollment Considerations

Co-enrollment in other studies is not precluded. However, careful consideration must be given to potential receipt of exclusionary medications and investigational agents as specified in Sections 4.2.2 and 4.2.3. Careful consideration must also be given to exposure to and half-lives of investigational products, visit burden, blood draw volumes, and interpretation of outcome data across studies. Given these considerations, requests for co-enrollment must be approved in advance by the Protocol Team of both studies. Requests for such approval should be emailed to the CMC.

4.5 Recruitment, Screening, and Enrollment Process

Recruitment methods for the study may vary across sites but are expected to rely on active identification and referral of children with probable or confirmed RR-TB. Based on current standards of care in locations where the study is expected to be implemented, children with RR-TB are typically diagnosed at hospitals (often referral centers), or at community-based TB clinics and may be treated in-hospital or at community-based TB clinics. Recruitment efforts may therefore be conducted in hospital-based or community-based settings. Study sites are expected to establish close communication procedures with local hospitals, TB clinics, and other TB programs to help identify potentially eligible participants; site-specific procedures will also include methods for identifying both participants living with HIV and participants living without HIV.

Upon identification of a potentially eligible participant, study staff will provide information about the study to the potential participant and/or the potential participant's parent/guardian as appropriate based on the age and maturity of the potential participant, guided by site SOPs and applicable IRB/EC policies and procedures. Potential participants/parents/guardians who express interest in learning more about the study will be provided additional information, education, and counseling as part of the study informed consent and assent processes. The informed consent process will include detailed review of the informed consent form and time to address any questions or concerns the potential participant/parent/guardian may have, as well as an assessment of understanding before proceeding to the informed consent decision. Potential participants who meet applicable IRB/EC criteria for providing assent will undergo an age-appropriate assent process. Informed consent and assent processes will be fully documented, consistent with the DAIDS policies referenced in Section 11.2. Refer to Section 13.3 for further information on informed consent and assent procedures for this study.

Eligibility screening will be initiated after written informed consent, and assent if applicable, are obtained (i.e., informed consent, and assent if applicable, must be obtained before any study-specific screening procedures are performed). Each site must establish SOPs for eligibility determination that describe where and when screening procedures will be performed; roles and

responsibilities for performing the required procedures; roles and responsibilities for assessing and confirming eligibility; and procedures for documenting the process, taking into consideration the required timing of enrollment.

Screening evaluations must be performed within 28 days prior to study entry and may be repeated during the 28-day period, with the latest outcomes used for eligibility determination. Screening evaluations may be performed on the day of enrollment (i.e., at the Day 0 (Entry) Visit); however, all required screening outcomes must be available for eligibility determination prior to enrollment.

Sites are encouraged to minimize the time from screening to enrollment. If at any time it is determined that a potential participant is not eligible for the study, or that study participation may not be feasible or in the potential participant's best interest, the eligibility screening process will be discontinued, with active referral to non-study sources of care.

The IMPAACT Data Management Center's (DMC) Study Enrollment System (SES) will be used to assist with tracking the screening and enrollment process, within and across the weight bands shown in Table 5. When informed consent is obtained, a participant identification number (PID) will be assigned, and a study-specific screening number will be obtained for the potential participant through the SES. For potential participants found to be eligible, enrollment will occur upon successful entry of required eligibility data into the SES. Successful entry into the SES will generate a study identification number (SID) and study drug prescribing information. For potential participants found to be ineligible for the study, or who do not enroll in the study for any reason, limited demographic information and reasons for non-enrollment will be entered into electronic case report forms (eCRFs). Refer to Section 9.5 for more information on monitoring participant accrual in this study.

4.6 Participant Retention

Once a participant is enrolled in this study, study staff will make every effort to retain the participant for the protocol-specified duration of follow-up, thereby minimizing potential biases and loss of statistical power associated with loss-to-follow-up. Refer to Section 9.5 for more information on monitoring participant retention in this study.

4.7 Participant Withdrawal or Termination from the Study

Regardless of the participant retention procedures referenced above, participants may voluntarily withdraw from the study or be withdrawn by their parents or guardians. Participants may also be terminated from the study early by the site investigator under the following circumstances:

- Participant is not exposed to pretomanid for any reason
- Participant re-locates away from the study site (with no options to transfer to another site) or is otherwise determined to be lost-to-follow-up
- Investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the participant, after consultation with the CMC
- The study is stopped or canceled by the sponsors or government or regulatory authorities
- Site participation in the study is canceled by the sponsors, government or regulatory authorities, or applicable IRBs/ECs

For any participant who withdraws, is withdrawn, or is terminated from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal or termination in detail.

5 STUDY DRUG

Site pharmacists should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations.

For this study, the term study drug refers to the formulations of pretomanid listed in Section 5.2. Refer to the IB for further information about the study drug.

Required TB OBR medicines are not considered study drug and will not be provided by the study.

5.1 Study Drug Regimen

A single, directly-observed dose of pretomanid will be administered to each participant with food by study staff at the Day 0 (Entry) Visit at the doses specified by weight in Table 5.

Table 5. Study Drug Regimen

Group	Weight	Formulation	Dose
1: ≥31 kg	≥40 kg	Adult	200 mg (one adult tablet)
	31-<40 kg	Dispersible pediatric	100 mg (two 50 mg dispersible tablets)
2: 20-<31 kg	20-<31 kg	Dispersible pediatric	100 mg (two 50 mg dispersible tablets)
3: 12-<20 kg	12-<20 kg	Dispersible pediatric	75 mg (one 50 mg dispersible tablet and half of one 50 mg dispersible tablet)
4: 4-<12 kg	8-<12 kg	Dispersible pediatric	50 mg (one 50 mg dispersible tablet)
	6-<8 kg	Dispersible pediatric	35 mg (half of one 50 mg dispersible tablet and one 10 mg dispersible tablet)
	4-<6 kg	Dispersible pediatric	20 mg (two 10 mg dispersible tablets)

5.2 Study Drug Formulations

The adult and pediatric formulations of pretomanid tablets, as well as the packaging and storage conditions, are described in Table 6.

Table 6. Study Drug Formulations

Adult or Pediatric	Formulation	Appearance	Debossing	Packaging	Storage in Study Site Pharmacy
Adult	200 mg tablet	White to off-white, oval shaped, uncoated	M on one side of the tablet and P200 on the other side	1 x 7 PVC/PVdC/ aluminum blister strips	Store in original packaging between 15–30°C (59–86°F)
Pediatric	10 mg dispersible tablet	Mottled light pink to pink, round, scored	One side of the tablet: M on one side of the score and P on other side of score Other side of the tablet: 1 on one side of the score and blank on the other side of the score	30-count with absorbent cotton in HDPE bottles with propylene child-resistant closures and with an induction seal liner	Store in original packaging between 20–25°C (68–77°F); excursions permitted between 15–30°C (59–86°F) *Dispersible tablets from an opened bottle may not be dispensed or administered past 90 days of opening. Once opened, the bottle must be marked with a do-not-use after date that is 90 days after opening.*
Pediatric	50 mg dispersible tablet	White to off-white, round, scored	One side of the tablet: M on one side of the score and P on other side of score Other side of the tablet: 5 on one side of the score and blank on the other side of the score		

PVC = polyvinyl chloride; PVdC = polyvinylidene chloride; HDPE = polyethylene

5.3 Study Drug Dispensing, Preparation, and Administration

5.3.1 Study Drug Dispensing

Pretomanid will be dispensed by the site pharmacist in a single pharmacy vial to study staff for administration to participants on the Day 0 (Entry) Visit. The dose will be dispensed based on weight in kilograms (Table 5). The pharmacy vial will be labeled with a participant-specific label.

Pretomanid 200 mg tablets

One pretomanid 200 mg tablet will be dispensed in the blister packaging within a pharmacy vial.

Pretomanid 10 mg and 50 mg dispersible tablets

Pretomanid 10 mg and 50 mg dispersible tablets are scored and can be cut in half at the score by using a pill splitter to obtain the appropriate dose to dispense. Pretomanid dispersible tablet(s) will be dispensed in a pharmacy vial along with a dosing cup and/or oral syringe.

Instructions on how to disperse the tablets and how the dispersed study dose is to be administered to the participant will be included.

5.3.2 Study Drug Preparation and Administration

A summary of dispersing, rinsing, and total volume consumed is presented in Table 7.

If a participant spits out the dose or vomits, the dose should not be repeated. See Section 6.2.1 for further details on procedural and sequencing requirements.

Pretomanid 200 mg tablets

One 200 mg pretomanid tablet will be administered to the participant orally with 200–240 mL ambient room temperature water. The tablet should be administered and swallowed intact and should not be crushed or chewed. The entire volume of administered water should ideally be consumed and should be entered into eCRFs.

Pretomanid 10 mg and 50 mg dispersible tablets

Immediately prior to administration, study staff should complete the following steps to prepare and administer the 10 mg and 50 mg dispersible tablets; study staff may include pharmacists or pharmacy technicians, nurses or clinicians, or other study staff trained to complete these procedures:

1. Premeasure the required dispersing volume of room temperature water (see Table 7) into a dosing cup.
2. Add the dispensed tablet(s) from a pharmacy vial to the cup of water.
3. Swirl the cup until the tablet(s) are dispersed completely.
4. Once the tablet(s) have fully dispersed, administer (or facilitate administration of) the entire volume of dispersing water within the cup to be immediately consumed by the participant.
5. Rinse the cup with up to a total of 20 mL (in divided portions, if needed) of premeasured room temperature water.
6. Administer (or facilitate administration of) the entire volume of rinsing water within the cup to be consumed by the participant. Enter into eCRFs the total rinsing volume consumed.

If necessary, instead of a cup, an oral syringe may be used to prepare and/or administer the dispersed drug and rinsing(s) from the cup.

Table 7. Dose Preparation and Administration Volumes per Group

Group	Weight	Dispersing Volume (mL)	Total Rinsing Volume (mL)	Total Volume Consumed (mL)
1: ≥31 kg	≥40 kg	NA	NA	200–240
	31-<40 kg	20	Up to 20	Up to 40
2: 20-<31 kg	20-<31 kg	20		Up to 40
3: 12-<20 kg	12-<20 kg	15		Up to 35
4: 4-<12 kg	8-<12 kg	10		Up to 30
	6-<8 kg	15		Up to 35
	4-<6 kg	20		Up to 40
NA=not applicable; enter into eCRFs the actual volume of total rinsing volume consumed Note: Participants in Group 1, ≥40 kg, will take one 200 mg tablet and swallow it with 200-240 mL water.				

5.4 Study Drug Supply

Pretomanid 200 mg tablets, pretomanid 10 mg dispersible tablets, and pretomanid 50 mg dispersible tablets will be manufactured by Mylan Laboratories Limited (A Viatris Company), supplied by TB Alliance, and made available to study sites through the NIAID Clinical Research Products Management Center (CRPMC). Upon successful completion of protocol registration procedures, study drug supplies may be obtained by site pharmacist following instructions provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

Ancillary supplies such as pill splitters, dosing cups, oral syringes, and pharmacy vials should be obtained locally by the site.

5.5 Study Drug Accountability

Site pharmacists must maintain complete records of all study drugs received from the CRPMC and subsequently dispensed.

5.6 Final Disposition of Study Drug

Any unused study drug will be destroyed. Site pharmacists will follow the relevant instructions for return or destruction of unused study products provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

5.7 Concomitant Medications

The term concomitant medications is used in this study to refer to medications other than the study drug listed in Section 5.1, i.e., other than pretomanid. This includes prescription and non-prescription (over-the-counter) medications, vaccines, and other preventive medications, contraceptives, antacids, vitamins and other nutritional supplements, and alternative, complementary, and traditional medications and preparations. All concomitant medications received by study participants will be source documented and entered into eCRFs as specified in Section 6.5.

5.8 Prohibited Medications

The site investigator or designee should consult with the CMC for any participant who requires a medication considered prohibited while on study, ideally in advance (or as soon as possible) of administration.

Pretomanid is partially metabolized by CYP3A4; as such, participants should not take strong or moderate CYP3A4 inhibitors (e.g., azole antifungals: ketoconazole, voriconazole, itraconazole, fluconazole; ketolides such as telithromycin; macrolide antibiotics other than azithromycin; ritonavir-boosted protease inhibitors [lopinavir or darunavir], atazanavir, and cobicistat) and inducers (e.g., rifamycins, efavirenz, etravirine, nevirapine, phenytoin, carbamazepine, phenobarbital, St. John's wort, and systemic dexamethasone) from two weeks prior to pretomanid administration until one week after pretomanid administration.

In addition, pretomanid may inhibit the OAT3 transporter; therefore, if an OAT3 substrate drug (e.g., methotrexate) is administered with or within one week after administration of pretomanid, monitor for OAT3 substrate drug-related adverse reactions, or consider dosage reduction for the OAT3 substrate drug.

6 STUDY VISITS AND PROCEDURES

An overview of the study visit and evaluation schedule is provided in Appendix I; blood draw volumes for each visit are also detailed in Appendix I. Presented in this section is additional information on visit-specific study procedures.

In addition to the protocol-specified procedures listed in this section, study staff may complete other tasks consistent with site SOPs, including but not limited to collecting, reviewing, and updating demographic and locator information; reviewing elements of informed consent and assent; scheduling visits; providing instructions for contacting study staff between visits; providing visit reminders; and following up on missed visits. All such tasks should be documented consistent with site SOPs. Study staff should inform participants/parents/guardians of clinically meaningful physical exam findings and laboratory test results when available.

All visits should be conducted as close as possible to specified target visit dates and within specified allowable visit windows. For visits with specified targeted windows, every effort should be made to conduct the visit within the targeted window. Unless otherwise specified, visits may be split, with required procedures performed on more than one day within the allowable visit window if necessary.

All visits and procedures must be documented in accordance with the DAIDS requirements for source documentation; refer to Section 11 for more information on documentation requirements and entry of eCRFs. Refer to Section 7 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up.

The extent to which site operations may be disrupted by COVID-19 may vary across sites and over time. All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff. All sites must also comply with any directives received from the study sponsor, the IMPAACT Network, and/or the IMPAACT 2034 Protocol Team. Sites are advised that screening and enrollment should only proceed if the site investigator has confidence that local conditions will allow for full study participation. In the absence of such confidence, screening and enrollment should not proceed. Sites should notify the CMC should any such pauses in screening or enrollment occur due to COVID-19 disruptions.

6.1 Screening Visit

Refer to Section 4.5 for a description of the study recruitment, screening, and enrollment process.

Screening procedures must be performed within 28 days prior to study entry. Multiple visits may be conducted within the 28-day time frame to complete all required procedures and to repeat laboratory tests, if necessary. Written informed consent, and assent if applicable, must be obtained before screening procedures are performed. For potential participants who do not meet the study eligibility criteria, screening should be discontinued once ineligibility is determined.

Additional requirements and guidance for screening evaluations are as follows:

- Creatinine testing is required in relation to the eligibility criterion in Section 4.1.7; as soon as the screening creatinine test result is obtained, the eGFR should be calculated using the bedside Schwartz equation, and all results should be graded for severity as specified in Section 7.3.3.
- HIV testing may or may not be required during the screening period per criterion 4.1.12 and testing options per Section 4.3. When testing is required, all required results must be available for eligibility determination prior to study entry.
- Pregnancy testing may or may not be required during the screening period per criterion 4.1.14. When testing is required, a blood or urine test may be performed; results must be available for eligibility determination prior to study entry.
- ECGs will be performed during the screening period; they should be reviewed by the site clinician in real time, but the central reading should be used to determine eligibility.
- Screening evaluations may be repeated, with the latest outcome used for eligibility determination, and as further specified in Section 4.1.

For potential participants who do not meet the eligibility criteria, screening may be discontinued once ineligibility is determined.

Screening Visit Procedures *(up to 28 days prior to enrollment)*		
Administrative and Regulatory		• Obtain written informed consent (additionally obtain written assent if applicable per IRB/EC policies and procedures) • Assign PID • Obtain screening number from SES
Clinical		• Obtain available documentation of participant's HIV status and TB status • Obtain available medical records and medical and medications history • Assess documentation of TB disease status, site of disease, and spectrum of disease • Assess documentation of resistance profile in relation to study requirements • Determine HIV status • Perform complete physical examination, including assessment of – MUAC (for children six months through five years of age) – Scores for Karnofsky (16 years of age and older) or Lansky (less than 16 years of age) • Perform ECG and interpret based on age-specific criteria
Laboratory	**Blood**	Collect blood for: • HIV-1 testing *if needed for determination of HIV status per inclusion criterion 4.1.12 and Section 4.3* • Complete blood count (CBC) with differential and platelets* • Chemistries: – Liver function tests (total bilirubin*, direct bilirubin, alkaline phosphatase, aspartate aminotransferase [AST], ALT*, and albumin) – Electrolytes (sodium, potassium, bicarbonate, chloride) – Glucose, calcium, blood urea nitrogen, creatinine*, total protein, lipase*
	Blood or Urine	Collect blood or urine for: • Pregnancy test *if needed per inclusion criterion 4.1.14*

*Required in relation to the eligibility criteria in Sections 4.1.7 and 4.1.8

Direct and total bilirubin are required at this visit. As soon as these results are obtained, indirect bilirubin should be calculated and assessed for clinical significance concurrent with all other laboratory test results (note there is no DAIDS-specified grading for indirect bilirubin).

In the event that the 28-day screening period is exceeded, the screening process may be repeated. In this case, all screening procedures listed above must be repeated, with the exception that:

- A new PID should not be assigned
- HIV testing need not be repeated for participants confirmed as living with HIV
- Previously documented medical and medications history information should be reviewed and updated through the date of re-screening (it is not necessary to re-record history information that was previously documented)

6.2 Intensive Pharmacokinetic Sampling Procedures: Days 0, 1, and 2

Eligible participants will enroll in the study and receive their single dose of pretomanid on Day 0 (Entry). PK sampling and other required study procedures will be performed on this day and continuing on Days 1 and 2, over a period of approximately 48 hours post-dose, as further described in Sections 6.2.1-6.2.3 and summarized in Table 8.

Depending on site capacity and participant/parent/guardian preferences, participants may stay at the clinical research facility (including overnight) for some or all of the required procedures. For example, a participant may stay at the facility through the 6-hour post-dose procedures and return separately for the 9-hour, 24-hour, and/or 48-hour post-dose procedures.

Table 8. Intensive PK Evaluation Sampling Time Points

Time Points	Hours Post-Dose					
	1	3	6	9	24	48
Window	±15 mins	±15 mins	±15 mins	±15 mins	± 4 hrs	± 4 hrs
Blood Volume	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL
Visit	Day 0				Day 1	Day 2
hrs=hours; mins=minutes						

6.2.1 Day 0 Visit (Entry)

Refer to Section 4.5 for a description of the study recruitment, screening, and enrollment process. Procedures that may provide information relevant to eligibility for the study (e.g., medical history, physical exam) should be performed first, prior to final eligibility determination. For potential participants found to be ineligible for the study on the scheduled day of enrollment, enrollment should not occur.

Additional requirements for sequencing of procedures at the Day 0 (Entry) visit are as follows:

- Final eligibility determination and confirmation must precede enrollment:
  - If pregnancy testing was required per inclusion criterion 4.1.14 at the Screening Visit, with results available for eligibility determination prior to enrollment.
  - Review centralized ECG read from screening evaluations to ensure eligibility per inclusion criterion 4.1.9 and exclusion criterion 4.2.4.2.
- Enrollment must precede prescribing of study drug.
- Prescribing must precede dispensing of study drug.
- Administering food, ideally a full meal, must occur within approximately 30 minutes before ingestion of study drug. *Note:* Breast milk qualifies as food for infants who are breastfeeding.
- Collecting blood for CBC with differential and platelets and chemistries must precede ingestion of study drug.
- Performing the pre-dose ECG must precede ingestion of study drug. A second ECG should subsequently be performed approximately six hours post-dose.
- Preparing, administering, and ingesting study drug must precede palatability and acceptability assessment.
- Completing palatability and acceptability assessment must occur within approximately 30 minutes after ingestion of study drug.

Day 0 *(Entry)* Visit Procedures		
Administrative and Regulatory		• Complete final eligibility determination and confirmation* • Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the participant, print and file a copy of the confirmation file
Clinical		• Obtain medical and medications history since last visit* (see Section 6.5) • *If applicable*, ascertain gender identity • Perform complete physical examination* • Perform ECG (pre- and approximately 6-hrs post-dose) and interpret based on age-specific criteria
Laboratory	**Blood**	Collect blood for: • CBC with differential and platelets† • Chemistries† – Liver function tests (total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin) – Electrolytes (sodium, potassium, bicarbonate, chloride) – Glucose, calcium, blood urea nitrogen, creatinine, total protein, lipase • Intensive PK evaluation, per Table 8: 1 mL at 1-, 3-, 6-, and 9-hours post-dose (4 mL total)
Study Drug		• Administer food, ideally a full meal, within approximately 30 minutes before ingestion of study drug (record details of food intake) • Prescribe, dispense, administer, and observe ingestion of study drug (record consumed water volumes) • Complete palatability and acceptability assessment within approximately 30 minutes after administration of study drug

**Perform prior to enrollment;* †CBC and chemistries are not required at Day 0 (Entry) if screening labs were drawn within three days.

Gender identity should be ascertained for participants 12 years of age and older. However, this procedure should not be performed at sites that have formally opted out of collection of gender identity data, in accordance with policies specified in the IMPAACT Manual of Procedures (MOP). Gender identity data should be collected from participants in private, without their parent or guardian present.

As noted in Section 5.3.2, there will be no redosing. If a participant spits out the dose of pretomanid or vomits within four hours after taking the dose, further PK sampling should be discontinued; all other study procedures, including all safety evaluations, should continue per Section 6 and Appendix I.

Creatinine testing is required at this visit. As soon as the creatinine result is obtained, the estimated eGFR should be calculated using the bedside Schwartz formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results. In addition, direct and total bilirubin are required at this visit. As soon as these results are obtained, indirect bilirubin should be calculated and assessed for clinical significance concurrent with all other laboratory test results (note there is no DAIDS-specified grading for indirect bilirubin).

Participants not staying overnight at the clinical research facility should be reminded to return the next day for the 24 hours post-dose visit.

6.2.2 Day 1 Visit

The Day 1 Visit is targeted to take place 24 hours following ingestion of pretomanid, with an allowable window of ± 4 hours (i.e., 20 to 28 hours post-dose).

There are no requirements for sequencing of procedures at this timepoint.

Day 1 Visit Procedures *(24 Hours ± 4 hours)*		
Clinical		• Obtain interval medical and medications history • Perform complete physical examination • Identify/review/update AEs • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	• Collect blood for intensive PK evaluation (1 mL, see Table 8)

Participants not staying overnight at the clinical research facility should be reminded to return the next day for the Day 2 visit.
ECG

6.2.3 Day 2 Visit

The Day 2 Visit is targeted to take place 48 hours following ingestion of pretomanid, with an allowable window of ± 4 hours (i.e., 44 to 52 hours post-dose).

There are no requirements for sequencing of procedures at this timepoint.

Day 2 Visit Procedures *(48 Hours ± 4 hours)*		
Clinical		• Obtain interval medical and medications history • Perform complete physical examination • Identify/review/update AEs • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • CBC with differential and platelets • Chemistries: – Liver function tests (total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin) – Electrolytes (sodium, potassium, bicarbonate, chloride) – Glucose, calcium, blood urea nitrogen, creatinine, total protein, lipase • Intensive PK evaluation (1 mL, see Table 8)

Creatinine testing is required at this visit. As soon as the creatinine result is obtained, the estimated eGFR should be calculated using the bedside Schwartz formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results. In addition, direct and total bilirubin are required at this visit. As soon as these results are obtained, indirect bilirubin should be calculated and assessed for clinical significance concurrent with all other laboratory test results (note there is no DAIDS-specified grading for indirect bilirubin).

Applicable reminders should be provided for the scheduled Week 2 Visit.

6.3 Week 2 Visit

The Week 2 Visit is targeted to take place on Day 14, counted from Day 0 (Entry), with an allowable window of ± 5 days. This visit is the final scheduled visit.

There is no required sequencing of procedures at this visit.

Week 2 Visit Procedures *(Day 14 ±5 Days)*		
Clinical		• Obtain interval medical and medications history • Perform complete physical examination • Identify/review/update AEs • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • CBC with differential and platelets • Chemistries: – Liver function tests (total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin) – Electrolytes (sodium, potassium, bicarbonate, chloride) – Glucose, calcium, blood urea nitrogen, creatinine, total protein, lipase

Creatinine testing is required at this visit. As soon as the creatinine result is obtained, the estimated eGFR should be calculated using the bedside Schwartz formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results. In addition, direct and total bilirubin are required at this visit. As soon as these results are obtained, indirect bilirubin should be calculated and assessed for clinical significance concurrent with all other laboratory test results (note there is no DAIDS-specified grading for indirect bilirubin).

At this visit, arrangements should be made to provide all clinically meaningful results to the participant/parent/guardian; these contacts should be documented in each participant's study chart but are not expected to be entered into eCRFs. The participant/parent/guardian should be informed of how to contact study staff with any post-study questions and how to learn about the results of the study when available.

6.4 Additional Follow-up After Week 2

Further participant management and eCRF data collection are required after the Week 2 visit in the following scenarios:

- If a participant becomes pregnant while on study: Refer to Section 8.3.2.
- If the participant has any grade 3 or grade 4 adverse event at the Week 2 visit: Refer to Section 8.1.2.

6.5 Medical and Medication History

Collection of medical and medication history information is required at each scheduled visit. A baseline history is established at the Screening and Day 0 (Entry) Visits and interval (since the last visit) medical and medications histories are obtained at follow-up visits. All history information may be obtained based on participant/parent/guardian report, but available medical records should also be obtained when possible to supplement reported information.

Documented medical conditions will be assessed for severity as described in Section 7.3.3 and new conditions occurring during follow-up will be assessed for relationship to study drug as described in Section 8.1. Relevant dates will be source documented for all conditions and medications; refer to Sections 5.7 and 5.8 for more information on concomitant and prohibited medications.

Table 9 specifies the baseline and interval medical and medications history elements that must be source documented, as well as associated eCRF entry requirements.

Table 9. Documentation Requirements for Medical and Medication Histories

Assess for and Source Document	Enter into eCRFs or SES
Baseline Medical and Medication History Elements	
Date of birth, sex at birth, race, ethnicity	Yes (all)
Gender identity (if applicable)	Yes
TB-related history: • Diagnoses, disease status, site of disease, and disease spectrum • Exposure history (ever) • Latent TB testing history (ever), e.g., tuberculin skin test (TST) or interferon-gamma release assay (IGRA) test • Treatment history (ever) • Current episode treatment history	Yes (all)
HIV status	Yes
If living with HIV, ARV use within the 28 days prior to enrollment	Yes (all)
History of allergy and/or hypersensitivity (including to anti-TB medications and, as applicable, ARVs)	Yes (all)
All medications taken within 28 days prior to enrollment	Yes (all)
Assessment of reproductive potential (has reached menarche, date of menarche if applicable), sexual activity, and contraception	Yes (all)
Any other information needed to determine eligibility for this study	No
Interval Concomitant Medical and Medication History Elements	
Current status of conditions that were ongoing at the previous visit	Any updates of previous entries (e.g., resolution dates)
Occurrence of any new conditions since the last visit	Any newly identified adverse events
Current status of medications that were ongoing at the previous visit	Any updates of previous entries (e.g., stop dates)
Use of any new medications since the last visit	Yes (all)
Assessment of reproductive potential, sexual activity, and contraception	All contraceptive methods used
For participants who become pregnant: pregnancy outcome, any congenital anomalies identified in the fetus or infant	Yes

6.6 Physical Examinations

Complete physical examinations are required at all indicated visits and should include the following:

- At the Screening Visit only:
  - Height
  - MUAC (for participants six months of age through five years of age)
  - Assessment of Karnofsky (16 years of age and older) or Lansky score (less than 16 years of age)
- Weight
- Vital signs, including temperature, pulse, and respiratory rate
- Age-appropriate neurological assessment
- Examination of:
  - Skin
  - Head
  - Eyes
  - Ears
  - Nose
  - Mouth and throat
  - Neck
  - Chest, including auscultation (heart and lung exam)
  - Abdomen
  - Extremities
  - Lymph nodes

At all visits, additional assessments may be performed at the discretion of the examining clinician.

All exam findings should be source documented and the following should be entered into eCRFs: height, weight, MUAC, and Karnofsky or Lansky score.

The Karnofsky Performance Status is a gold standard scale used in people over the age of 16 years. It is a simple and rapid method to assess the ability of patients to perform ordinary tasks and allows patients to be classified as to their functional impairment. It can be used to compare effectiveness of different therapies and to assess the prognosis of individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.(35) Similarly, the Lansky play-performance scale is a parent-rated instrument which records usual play activity as the index of performance.(36)

At the Screening Visit, the measurements listed above should be used to determine weight-for-height z-scores (for children up to and including five years of age) or body mass index z-scores (for children older than five years of age), which will be assessed in relation to WHO growth standards. These scores and the associated severity grade should also be source documented and entered into eCRFs. At the entry visit and all subsequent follow-up visits, weight will be measured; z-scores will not be calculated at these visits, but participant weight will be monitored throughout follow-up, with severity grading for unintentional weight loss, should such weight loss occur.

In addition to the above, abnormal findings identified prior to enrollment will be entered into medical history eCRFs. Abnormal findings identified after enrollment will be entered into adverse events eCRFs as specified in Section 7.2.

6.7 Electrocardiograms

Electrocardiograms (ECGs) will be performed during the screening period to meet inclusion criterion 4.1.9 and to evaluate exclusion criterion 4.2.4.2; ECGs will also be performed at the Day 0 (Entry) Visit pre-dose and approximately six hours post-dose as noted in Section 6.2.1. ECGs must be performed on machines programmed for the study.

ECGs will be reviewed based on age-specific criteria by site clinicians in real time to assess for clinical relevance and identification of any safety problems that require urgent intervention, including an assessment of QT (QTcF) interval. Mean QT interval will be calculated at sites based on triplicate ECG readings (three consecutive ECGs) at each time point. If it is not possible to obtain a triplicate ECG reading, at a minimum one high quality ECG reading should be obtained at each required time point as indicated in Appendix I. Consult the CMC for any questions on ECG quality. All results will be source documented and all results, regardless of grade, will be entered into eCRFs.

All ECGs will also be read centrally, and central readings will be used to determine eligibility, final adverse event reporting, clinical management, and statistical analyses. Following receipt of the centralized ECG reading, generally within three to five days of transmission, further clinical management should be performed based on the AE grade from the centralized read. Refer to Sections 7.3.3 and 8.1, respectively, for more information on grading and management of abnormal ECG results.

To ensure appropriate safety monitoring by the CMC, ECG AEs should be entered in appropriate eCRFs upon availability of the relevant clinical findings and test results from the site. Following receipt of the centralized read, sites should review and confirm that the results for ECG AEs entered in eCRFs are consistent with the results based on the centralized read.

6.8 Palatability and Acceptability Assessment

A study-specific form will be used to assess palatability and acceptability of the study formulations of pretomanid. Palatability and acceptability will be assessed during the Day 0 (Entry) Visit, within approximately 30 minutes after ingestion of the single dose of pretomanid and may include participant and/or parent/guardian opinion on the size and shape of the tablets, overall taste, and/or ease of swallowing.

Study staff should ideally administer the assessment to the participant, with the parent/guardian assisting as needed; however, if a participant is too young or is otherwise unable to complete the assessment, sites should administer the assessment to the participant's parent/guardian. If neither the participant nor the participant's parent/guardian can complete the assessment, study staff who were present at the time of administration and ingestion should complete the form. Study staff should enter into eCRFs to whom the assessment was administered and all assessment data.

6.9 Additional Considerations for Laboratory Procedures

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at:

https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management

6.9.1 Specimen Collection

Specimens will be collected for this study as indicated in the Schedule of Evaluations and per detailed guidance provided in the Laboratory Processing Chart (LPC), which will be available on the study-specific website:

https://www.impaactnetwork.org/studies/impaact2034

Consistent with US National Institutes of Health (NIH) Guidelines for Limits of Blood Drawn for Research Purposes at the NIH Clinical Center, pediatric blood collection will not exceed 5 mL/kg in a single day or 9.5 mL/kg in any eight-week period.

If blood collection must be limited to complete required screening evaluations, samples should be collected at different time points throughout the allowable screening window. In the event that blood collection must be limited from Day 0 (Entry) through Week 2, available specimens should be prioritized for use in the following order: (1) PK, (2) chemistries, and (3) CBC with differential and platelets.

6.9.2 Specimen Preparation, Testing, Storage, and Shipping

All specimens collected for this study will be labeled, transported, processed, tested, stored and/or shipped in accordance with the DAIDS policy referenced in Section 6.9, site and local laboratory SOPs, and the LPC. The frequency of specimen collection and testing will be directed by the Schedule of Evaluations in Appendix I and specifications for clinical management provided in Section 8. The Laboratory Data Management System (LDMS) will be used to document specimen collection, testing, storage, and shipping as specified in the LPC. Any specimens stored at the Screening Visit for participants who do not subsequently enroll in the study will be destroyed.

If HIV testing is needed, assays must be performed following laboratory operations requirements (e.g., GCLP, or VQA) and regulatory authority approvals (e.g., FDA) as specified in Section 4.3.

Specimens collected, processed, and stored at site laboratories for intensive PK evaluations are expected to be shipped approximately every three months, based on sample stability limits, to the designated testing laboratory; samples may also be requested for more rapid shipment prior to the interim analysis and at the end of the study. Depending on the rate of accrual, intensive PK samples may be tested every three months, as received from sites, or at the time for the interim analysis and after all intensive PK samples have been collected.

After all protocol-specified laboratory testing has been performed, remaining, extra specimens will be destroyed; there will be no option for future research use.

6.9.3 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the US Centers for Disease Control and Prevention (CDC), NIH, and other applicable agencies. All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for UN 2814 Category A Infectious Substances.

Respiratory pathogens such as *Mtb* and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are transmitted by inhalation of droplet nuclei. Appropriate precautions will be employed by all personnel in participant management and the collection of clinical samples and the shipping and handling of all clinical samples and isolates for this study, as currently recommended by the CDC and the NIH.

7 SAFETY ASSESSMENT, MONITORING, AND REPORTING

Participant safety will be carefully assessed, monitored, and reported at multiple levels throughout this study. Sections 7.1-7.3 describe safety-related roles, responsibilities, and procedures for site investigators. The safety monitoring roles of the CMC and the IMPAACT SMC are briefly referenced in Section 7.1 and described in greater detail in Sections 9.5.1 and 9.5.2.

7.1 Safety-Related Roles and Responsibilities

7.1.1 Site Investigators

Site investigators are responsible for continuous monitoring of all study participants and for alerting the Protocol Team if unexpected concerns arise. Site investigators will enter safety-related data into eCRFs as indicated in Section 7.2 and complete EAE reporting as indicated in Section 7.3.

Site investigators are also responsible for prompt reporting of any unanticipated problems involving risks to participants or others to all applicable IRBs/ECs and other applicable review bodies, per the procedures of each applicable review body.

7.1.2 Clinical Management Committee (CMC)

The following Protocol Team members comprise the CMC: Chair, Vice Chairs, Medical Officers, Pharmacologist, Statisticians, Protocol and Laboratory Data Managers, Clinical Research Managers, and selected representatives from TB Alliance; other selected Protocol Team members may also be included in the CMC as needed. The CMC will provide guidance as needed to site investigators regarding all aspects of participant management, including but not limited to questions of participant eligibility and management of adverse events, study drug regimens, and concomitant medications. Refer to Section 8 for more information on participant management.

On behalf of the full Protocol Team, the CMC will monitor study progress, quality of study conduct, and participant safety through routine review of study data reports as described in Section 9.5.1.

7.1.3 Study Monitoring Committee (SMC)

An independent IMPAACT SMC will monitor participant safety through routine and as needed reviews of study data. Refer to Section 9.5.2 for more information on the role of the SMC in monitoring this study.

7.2 Safety-Related Data Collection

Note: This section describes eCRF data collection for pre-existing conditions, adverse events, and laboratory test results. As part of this description, reference is made to severity grading and criteria for EAE reporting; refer to Sections 7.3.3 and 7.3.2, respectively, for detailed information on these topics.

The definition of the term adverse event provided in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual) will be used in this study. This definition will be applied to all participants, beginning after ingestion of study drug. Any untoward medical conditions identified prior to enrollment will be considered pre-existing conditions. Refer to Section 4.5 for more information on defining the effective point of enrollment in the study.

Pre-Existing Conditions

All pre-existing conditions (i.e., all grade 1 or higher) identified during the 28 days prior to study entry will be entered into medical history eCRFs. Among other details, the severity of all such conditions will be entered into these eCRFs.

Adverse Events

All adverse events (i.e., all grade 1 or higher) identified after ingestion of study drug will be entered into adverse event eCRFs.

Laboratory Test Results

All safety-related laboratory test results will be entered into laboratory eCRFs, regardless of severity grade and regardless of whether the test was protocol-specified or ordered by the site investigator for clinical purposes.

All pregnancy test results will also be entered into laboratory eCRFs; HIV-1 RNA will be entered into laboratory eCRFs or transferred electronically to the DMC through the LDMS.

As noted in Section 6.7, results of all ECGs will be entered into eCRFs.

7.3 Expedited Adverse Event (EAE) Reporting

7.3.1 EAE Reporting to DAIDS

Requirements, definitions, and methods for expedited reporting of adverse events are outlined in Version 2.0 of the DAIDS EAE Manual, which is available at:

https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available at: https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

For questions about DAERS, please contact NIAID Clinical Research Management System (CRMS) Support at: CRMSSupport@niaid.nih.gov.

Queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS Regulatory Support Center (RSC) Safety Office at: DAIDSRSCSafetyOffice@tech-res.com.

7.3.2 EAE Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. In addition to the SAE Reporting Category, other adverse events that must be reported in an expedited manner are:

- Suicidal ideations or attempts
- Seizures
- Stillbirth
- Spontaneous abortion or miscarriage

The study product for which expedited reporting is required is pretomanid.

7.3.3 Grading Severity of Events (applies to EAEs and all other adverse events)

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated July 2017, will be used in this study. This table is available at:

https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables

The DAIDS AE Grading Table provides grading for prolonged QTc interval assessed per Bazett's formula (QTcB); in IMPAACT 2034, prolonged QTc interval should be assessed using the DAIDS-indicated parameters for prolonged QTc interval but corrected per Fridericia's formula (QTcF).

The DAIDS AE Grading Table provides grading for creatinine and eGFR values based on both absolute value and change from baseline. For this study, only the grading based on absolute value should be used.

The DAIDS AE Grading Table parameter for underweight uses WHO z-scores, which may not be appropriate thresholds for this study. Therefore, assessment of underweight will only be evaluated at screening, in relation to eligibility criteria; however, as noted in Section 6.6, participant weight will be monitored throughout follow-up, with severity grading for unintentional weight loss, should such weight loss occur.

7.3.4 EAE Reporting Period

The EAE reporting period for this study begins at the time of ingesting the pretomanid dose and continues through the Week 2 visit.

After the protocol-defined EAE reporting period, and except for the selected pregnancy outcomes as noted in Section 7.3.2 above, only suspected unexpected serious adverse reactions (SUSARs) as defined in Version 2.0 of the DAIDS EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8 PARTICIPANT MANAGEMENT

Guidance and requirements for management of adverse events are presented in Section 8.1, with criteria for premature discontinuation presented in Section 8.2. Guidance and requirements for contraception, pregnancy testing, and management of participants who become pregnant are presented in Section 8.3.

8.1 Management of Adverse Events

All adverse events identified in this study will be source documented in participant research records, consistent with the requirements referenced in Section 11. Among other details, source documentation will include the severity of each event (graded as described in Section 7.3.3) and its relationship to study product, assessed by the site clinician according to the following categories and definitions:

Related There is a reasonable possibility that the adverse event may be related to pretomanid

Not related There is not a reasonable possibility that the adverse event may be related to pretomanid

Further standardized guidance on determining whether there is a reasonable possibility of a relationship is available in the DAIDS EAE Manual, referenced in Section 7.3.1.

Adverse events will be managed based on their severity and assessed relationship to study drug. Additional evaluations beyond those listed in Appendix I may be performed at the discretion of the site investigator to determine the etiology of a given event and/or further assess its severity or relationship to study drug. Clinical management of all adverse events should be provided consistent with the best medical judgment of the site investigator and local clinical practice standards.

In the event of any adverse event that results in death (fatal) or is life-threatening and is assessed by the site investigator as related to study drug, the CMC should be contacted as soon as possible and within three business days of site awareness, consistent with the potential triggers for SMC review described in Section 9.5.2.

Site investigators should carefully consider adverse events in relation to pretomanid, as described in the IB. Of note, site investigators should closely monitor any signs or symptoms consistent with hepatotoxicity and QT interval prolongation; however, multiple other TB medicines are known to cause hepatotoxicity as well as QT interval prolongation, making establishment of causality challenging. Site investigators should consider all medications that the participant may be taking or has been recently exposed to, as well as any other causes when determining potential management plans. Site investigators should also work closely with non-study clinical care providers to consider modifications to the TB OBR regimen, as clinically indicated.

- *Hepatoxicity:* Site investigators may consider repeating liver function tests (LFTs), including ALT, AST, and bilirubin, as well as testing for other possible causes (e.g., viral hepatitis), consistent with local standards of care.
- *QT interval prolongation:* Other potential causes of QT prolongation include other concomitant medications and electrolyte abnormalities, including from significant vomiting or diarrhea. Site investigators may consider checking electrolytes (potassium, magnesium, and calcium) and address findings as necessary.

8.1.1 Management of Grade 1 or Grade 2 Adverse Events

All grade 1 and grade 2 adverse events should be monitored at the discretion of the site investigator; consultation with the CMC is available but not required.

If the AE is not resolved or stabilized by Week 2, site investigators should refer participants to local, non-study sources of care and treatment to manage these adverse events following study completion at Week 2.

8.1.2 Management of Grade 3 or Grade 4 Adverse Events

Upon initial identification of a grade 3 or grade 4 adverse event, notify CMC within three business days; consider and investigate non-study drug explanations for the event, in consultation with the CMC.

If the initial grade 3 or 4 event is a laboratory result, repeat the test as soon as possible (and within three business days of site's awareness). If the repeat test is grade 1 or 2, the event should be managed according to Section 8.1.1, above.

Frequency of other repeat evaluations should be determined by the clinical significance of the event, until improvement to grade 2 or lower, or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator and in consultation with the CMC.

If the participant has any grade 3 or grade 4 adverse event that is ongoing or newly identified at the Week 2 visit, the participant should be asked to continue on study for up to 30 days following ingestion of pretomanid or until resolution (return to baseline) or stabilization, whichever is sooner, with the frequency of visits determined by the site investigator in consultation with the CMC. Participants should subsequently be referred to local non-study sources of care and treatment to manage the adverse events following study completion.

8.2 Criteria for Premature Discontinuation of Study Drug

There are no criteria for premature discontinuation of study drug, as this study involves only one dose of study drug.

8.3 Contraception, Pregnancy Testing, and Management of Participants Who Become Pregnant on Study

Reproductive history, sexual activity, contraception use, and pregnancy test results may or may not be disclosed to parents/guardians; requirements and standard practices related to disclosure will be consistent with local standards of care and local standard procedures will be noted in site-specific informed consent and assent forms. In settings where disclosure to parents/guardians will be at the choice of the participant, participants will be counseled that proactive (rather than potential inadvertent) disclosure to parents/guardians may be advised.

8.3.1 Contraception and Pregnancy Testing

At the Day 0 (Entry) visit but prior to enrollment, all participants must meet the contraception and pregnancy testing requirements as described in Sections 4.1.14–4.1.15. If required per Section 4.1.14, pregnancy testing should be performed during the study screening period, with results available prior to enrollment to confirm eligibility. Medical history information, including reproductive history, sexual activity, and contraception use, when applicable, will be collected at each scheduled visit. Date of menarche will be recorded in source documents when applicable.

During study participation, all participants should be provided with contraception counseling, as applicable, and consistent with requirements in Section 4.1.15. Sites should reinforce directions related to use of effective, medically accepted contraception methods and all participants who have reached menarche or who are engaging in sexual activity that could lead to their pregnancy should be counseled about NOT becoming pregnant while in the study. For participants engaging in sexual activity, self-reported confirmation of contraception use should be obtained at every visit. These discussions should be source documented in research records. If participants engaging in sexual activity report discontinuation of contraception use, the site should consult the CMC on further management.

Counseling should be provided per site SOPs, which should reflect WHO guidelines for individuals with and without HIV as well as local standards of care. Counseling should reflect the anti-TB medications and, as applicable, ARVs that participants are currently taking and the potential interactions between these medications and available contraceptive methods. Study sites should ideally integrate provision of contraceptive methods with other services offered to study

participants and should provide referrals to non-study sources of methods that cannot be provided at the study site. All participants will be counseled about use of condoms. Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV-1 transmission.

Pregnancy testing will be performed among participants who have reached menarche or who are engaging in sexual activity at any time if clinical indicated (i.e., pregnancy is suspected). Pregnancy test results will be entered into eCRFs.

8.3.2 Management of Participants who Become Pregnant on Study

As described in Section 1.2.2.2, testicular degeneration/atrophy has occurred in rats with repeated doses of pretomanid but did not occur in monkeys at any dose level. In human males, evaluation of reproductive hormones did not show a change following exposure to pretomanid (Section 1.2.6); however, there is an ongoing study in adult humans to further evaluate testicular toxicity. As noted above in Section 8.3.1, participants will be screened to avoid enrolling a participant who is pregnant and will be counseled to use contraception. However, given these potentials concerns, any participants reporting pregnancy during the study period will remain on-study until their pregnancy outcome is ascertained per Section 6.4.

Any participant who becomes pregnant (intrauterine) should be referred to appropriate non-study care and treatment, with information, counseling, and/or referrals provided as needed. Any pregnancy that occurs during study participation must be reported to the CMC immediately (within 24 hours of site awareness). Participants/parents/guardians will be contacted after the Week 2 visit to ascertain the pregnancy outcome (Section 6.4). Adverse pregnancy outcomes, including intrauterine fetal demise, spontaneous abortions, or therapeutic or otherwise medically indicated abortions, should be reported to the CMC immediately (within 24 hours of site awareness); stillbirths as well as spontaneous abortions or miscarriages should be reported as an EAE, consistent with the requirements as indicated in Section 7.3.2. Outcomes may be ascertained based on participant/parent/guardian report, but medical records should be obtained whenever possible to supplement participant/parent/guardian reports.

Study sites are encouraged to prospectively register participants living with HIV who become pregnant in the Antiretroviral Pregnancy Registry prior to pregnancy outcome by calling the following number in the US: +1-800-258-4263. Outside of the US, see the Antiretroviral Pregnancy Registry website (www.apregistry.com) for additional toll-free numbers.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Refer to Section 3 for a complete description of the study design and to Section 9.4 for a description of the study accrual plan.

This statistical section describes the methodology and analyses for the secondary safety objective and secondary non-PK objective only. Refer to Section 10 for methodology and analyses planned for the primary and exploratory PK objectives. Refer to Section 9.6 for a description of the planned analyses and to Section 3 for definitions of PK and safety evaluability. The primary

analysis will be performed when all participant data from intensive PK samples are available (i.e., through Day 2).

This study can only provide minimal information on safety of pretomanid in children with RR-TB, that is, safety of a single dose of pretomanid under the protocol-specified dosing level and taken while on an OBR. It will not reflect patient safety under multiple dosing at the optimal level, which would be the anticipated use of pretomanid as part of a regimen for TB treatment in clinical settings.

9.2 Outcome Measures

Note: The numbering of the outcome measures in this section corresponds to the numbering of the objectives in Section 2.

Primary outcome measures are listed in Section 10.2.1 and will be addressed in a separate PK Statistical Analysis Plan (SAP); secondary outcome measures listed below will be addressed in the study's primary SAP. Together, these plans will define the content of the primary analysis report(s). These report(s) will form the basis for the primary study manuscript and results reporting to ClinicalTrials.gov.

9.2.1	**Primary Outcome Measures**
9.2.1.1	• See Section 10.2.1
9.2.2	**Secondary Outcome Measures**
9.2.2.1	• All adverse events • Grade 3 or higher adverse events • Grade 2 or higher adverse events assessed as related to study drug • All serious adverse events
9.2.2.2	• Parent/guardian and/or participant (and/or study staff) reported palatability and acceptability of study drug given as single dose at entry
9.2.3	**Exploratory Outcome Measures**
9.2.3.1	• See Section 10.2.3

9.3 Randomization and Stratification

Participants will be enrolled in the four weight-based groups at the study Day 0 (Entry) Visit. There will be no randomization in this single arm study.

9.4 Sample Size and Accrual

9.4.1 Sample Size

The sample size of at least 36 evaluable participants, with at least nine in each weight-based group, is primarily based on PK considerations and in alignment with requirements of the agreed PIP. Clinical trial simulations were performed to ensure a sample size able to provide precise enough identification of weight-based doses. Refer to Section 10 for details regarding this. There will be an attempt to enroll at least three evaluable participants who are less than 8 kg to help ensure availability of PK data for smaller children. A total sample size of up to 72 participants has been specified to ensure that the minimum required number of evaluable (see Section 3) children

are enrolled within each group (assuming 15% non-evaluability rate) and to accommodate an increase in target sample size as determined from one interim analysis of the PK and safety data.

Table 10 presents 90% confidence intervals, using Wilson score method without Yates continuity correction, around various potential rates of grade 3 AEs or higher (or a safety outcome measure specified in Section 9.2.2.1), which might be observed in a total sample of 36 participants who might contribute data to the primary safety analysis, and a sample of nine participants within a weight-based group. This table indicates that confidence intervals will be quite wide around the sample size of nine participants per group and, as expected, would be narrower around the total sample size of 36 for all participants across groups.

Table 10. Percent of Participants Experiencing a Safety Outcome with 90% Confidence Intervals*

Number of Children	Number of Safety Failures	Proportion of Safety Failures
9	0	0.00 (0.00, 0.23)
	1	0.11 (0.03, 0.38)
	2	0.22 (0.08, 0.50)
	4	0.44 (0.22, 0.70)
36	0	0.00 (0.00, 0.07)
	4	0.11 (0.05, 0.23)
	8	0.22 (0.13, 0.35)
	16	0.44 (0.32, 0.58)
*Calculated using Wilson score method without Yates continuity correction		

9.4.2 Accrual

Accrual is expected to be completed approximately 24-36 months from the date the first participant is enrolled, and participants in all groups will be followed for two weeks. Hence, the expected duration of the study is 25-37 months after the first participant is enrolled. Accrual to all groups will occur in parallel.

There is no planned study accrual pause, including during the interim analysis of PK data. Accrual into the study will remain open while the interim analysis is being completed and data are being reviewed by the CMC and SMC. However, the number of participants enrolled will not exceed the targeted number evaluable for each group.

A minimum of nine evaluable participants, with an attempt to enroll three evaluable participants less than 8 kg, will be enrolled in each group, for a minimum overall target accrual of 36 evaluable participants. Refer to Section 3 for a detailed description of criteria for evaluability, which includes criteria for both PK and safety evaluations.

The accrual target may be increased as determined by evaluation of PK data during interim analysis, with an allowed enrollment of up to 72 participants.

9.5 Monitoring

Implementation of this study will be monitored at multiple levels, consistent with standard IMPAACT procedures. A study monitoring plan that details monitoring roles and responsibilities and data to be reviewed at each level will be prepared before the study opens to accrual. Sections 11 and 12 provide for more information on on-site monitoring and quality management at the site

level. Further information on monitoring of study progress, quality of study conduct, and participant safety across sites is provided below.

9.5.1 Monitoring by the Protocol Team

Study Progress and Quality of Study Conduct

The Protocol Team is responsible for continuous monitoring of study progress, including timely achievement of key milestones, and quality of study conduct.

The Protocol Team will monitor participant accrual based on reports that will be generated at least monthly by the Statistical and Data Management Center (SDMC). The team has developed a study accrual plan that includes site-specific and total enrollment projections over the course of the accrual period, and actual accrual will be monitored relative to these projections.

The Protocol Team will monitor the timing of site-specific study activation, which will determine when each site begins accruing participants, and actual accrual following activation. The number of potential participants screened, reasons for screen failures, and number of participants enrolled by each weight group and sub-set noted in Table 5 will be closely monitored. Accrual performance will be reported by the DMC, by site and across sites, and the team will review and discuss study progress at least monthly. For any site that is delayed in completing the study activation process, or that falls short of its accrual projections, the team will communicate with the site to identify the barriers the site has encountered and the operational strategies and action plans to address these. The Protocol Team will also monitor participant retention.

On behalf of the Protocol Team, the CMC will monitor other key indicators of the quality of study conduct (e.g., adherence to study drug regimen, data quality, and data and specimen completeness, protocol deviations). This monitoring will be based on reports generated by the SDMC, and CMC members will take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation.

Participant Safety

On behalf of the Protocol Team, the CMC will closely monitor participant safety through routine review of safety data reports generated by the SDMC. These reports will be based on the safety-related data collection described in Section 7.2 and will provide listings and/or tabulations of adverse events and laboratory test results. The CMC will review these reports at least monthly. At the time of each review, the DAIDS Medical Officer will also review any EAEs reported to the DAIDS Safety Office that are not yet reflected in the data reports. The CMC will continually evaluate the pattern and frequency of reported events and assess for any individual occurrences or trends of concern. The CMC will also monitor for the occurrence of adverse events meeting criteria to pause participant accrual and/or convene an ad hoc SMC review, as described in the remainder of this section and in Section 9.5.2.

Interim Analysis for Sample Size Reassessment

An interim analysis to re-assess sample size upwards (i.e., only an increase will be considered) will be performed once at least 12 PK-evaluable participants in Groups 1 and 2 AND at least 12 PK-evaluable participants in Groups 3 and 4 have been enrolled and completed PK sampling. All participants with available PK samples, including from those who were determined to be PK-

unevaluable, will be included in the PK interim analysis; all participants with available safety data, including from those who were determined to be safety-unevaluable, will also be included. Details of the interim PK analysis, and guidelines for reassessment of sample size adequacy, are described in Section 10.4. Accrual into the study will remain open while the interim analysis is being completed and data are being reviewed by the CMC and SMC. However, the number of participants enrolled will not exceed the targeted number evaluable for each group. If the target sample size of 36 PK-evaluable participants is deemed sufficient, no changes will be made; otherwise, the number of evaluable participants will be increased beyond the initial target of nine in a group, where needed. In addition, this scheduled interim PK analysis will take into account loss of PK data due to quality of the sample. Hence, any determination to increase sample size beyond the initial target may also figure in anticipated loss of PK data, based on observed losses from the available data at the time of the interim analysis.

9.5.2 Monitoring by the SMC

An independent IMPAACT SMC will review this study regularly, following policies described in the IMPAACT MOP.

The first SMC review of study data will occur approximately six months after the first participant is enrolled. Thereafter, SMC reviews will occur at least annually and may also occur on a more frequent or ad hoc basis if any safety issues or concerns arise, or if requested by the SMC or CMC. Reviews will focus on participant accrual, retention, study conduct, and safety. An SMC review of safety and PK data used for sample size re-assessment during the interim analysis will also take place. Additional SMC reviews focused on safety may also be triggered per the safety monitoring guidelines specified below. Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges that may be identified during their reviews.

Study Progress and Quality of Study Conduct

The SMC will monitor study progress and quality of study conduct. The SMC will generally review the same types of data reports as the Protocol Team and CMC.

Participant Safety

The SMC will monitor participant safety through review of similar types of safety data reports as the CMC. For ad hoc or triggered safety reviews, more limited data may be reviewed, focusing on the events that triggered the reviews.

Triggered SMC reviews will occur in the following scenarios:

(1) In the event of any fatal or life-threatening adverse event, assessed by the site investigator as related to study drug, the CMC will pause accrual into all groups as soon as possible (ideally within three business days of site awareness). An ad hoc SMC review will be convened as soon as possible to discuss how the study should proceed.
(2) In the event that at least two participants in the same group experience the same grade 3 or grade 4, non-life-threatening adverse event, assessed by the site investigator as related to study drug, the CMC will review, and an ad hoc SMC review will be convened as soon as possible. The SMC will review all relevant safety and PK data, along with any

recommendations from the CMC, to discuss how the study should proceed. Following an initial triggered SMC review, if additional participants in the same group experience the same grade 3 or grade 4, non-life-threatening adverse event, assessed as related to study drug, another SMC review will be convened. These triggers will be monitored by the CMC through routine monitoring (Section 9.5.1) and through real-time review of site communications with the CMC.

If the CMC has questions about or disagrees with the site investigator's assessment of relationship to study drug, the CMC will discuss the adverse event further with the site investigator and ideally come to consensus with the investigator.

If the CMC encounters any other event or trend of concern (for example, patterns of the same grade 2 or higher adverse event), an SMC review of the relevant data will be convened. The CMC may choose to pause participant accrual, pending the outcome of the SMC review.

Table 11 shows the probability of a triggered SMC review given various assumed true probabilities that a participant experiences the events above.

As shown in the table below, there is at least 70% probability that the safety trigger will be met if the true toxicity rate is 25% or higher in a specified group, and at most 56% probability that a safety trigger will be met if the true toxicity rate is 20% or less. A true toxicity rate of 25% would be of concern for a drug indicated for treatment of MDR-TB.

Interim Analysis

Following the CMC's review of interim analysis for sample size reassessment as described above in Section 9.5.1, the CMC will prepare a summary report for the SMC. The SMC will then have the option to review the CMC's notification via email or to convene a review before providing a recommendation with respect to the CMC's outcome or assessing next steps for the study.

Table 11. Probability that SMC Review is Triggered Based on Number (X) and Observed Proportion of Participants with the Same Drug-Related Grade 3 or Grade 4 Non-Life-Threatening Adverse Event for a Given Sample Size (N) and True Event Probability*

Participants →	N=9		
Threshold X: (Obs. %) →	X=1 (11%)	X=2 (22%)	X=3 (33%)
True Prob. Grade 3 or 4 Non-Life-Threatening AE			
50%	>99%	98%	91%
25%	92%	70%	40%
20%	87%	56%	26%
15%	77%	40%	14%
10%	61%	23%	5%
8%	53%	16%	3%
6%	43%	10%	1%
5%	37%	7%	1%
4%	31%	5%	<1%
3%	24%	3%	<1%
2%	**17%**	**1%**	**<1%**

*Assume as well that true probability of drug-related death or life-threatening adverse event is very rare (almost 0%) and having at least one drug-related death or life-threatening adverse event is also a safety trigger.
Note that probabilities in the table may be higher if true probability of drug-related death or life-threatening adverse event is greater than zero.

9.6 Analyses

There are two separate final analysis reports that will be prepared for this study. A final PK analysis report will be prepared by the pharmacometrician to address the primary objective of the study. Another final analysis report will be prepared by the statisticians to address the secondary objectives of the study.

9.6.1 Primary Analyses

The primary analyses will focus on the primary PK objective and will be performed by the study pharmacometricians. Refer to Section 10.5 for the analysis plan.

9.6.2 Secondary Analyses

Safety and Tolerability

The key (main) safety analyses will focus on the two-week time period following the single dose administration of pretomanid at the Day 0 (Entry) Visit. For these analyses, participants who did not receive the single dose of the study drug and did not complete the two-week follow-up period (unless they experienced the safety outcome) will be excluded from the analysis set.

The proportions of participants experiencing each of the outcome measures listed in Section 9.2 will be presented in aggregate and broken down by group, as well as by HIV status overall (across all groups) and within each group (if sample size allows), with these proportions bounded by 90% confidence intervals using the Wilson score method without Yates continuity correction.

Note that safety interpretations on these proportions should be limited only to the specific doses these participants received, and in a single dose, and do not necessarily reflect the safety profile of pretomanid under a dose and regimen that will be recommended for clinical use.

Sensitivity analyses will also be performed and will include participants who have received the single dose of pretomanid while on study. Those who have left the study prior to two weeks post-study drug administration and did not reach the safety outcome measure of interest will be analyzed in at least two ways: (1) safety failures (worst case); and (2) not safety failures (best case).

Given that the small sample sizes within groups will provide limited power for statistical tests of differences across groups, interpretation of differences across groups will depend upon whether these differences are large enough to be considered clinically significant. If no such differences are observed, then the clearest interpretation of the findings will come from the aggregated data, where analyses will have greatest statistical precision. However, if results vary across groups to a clinically important extent, interpretation of results should take into account the weight differences and potential treatment differences represented by this stratification factor.

Details concerning the analyses will be included in a separate statistical analysis plan.

Palatability and Acceptability Outcomes

Acceptability and palatability will be summarized overall, by group, as well as by HIV status overall (across groups) and within group (if sample size allows). For each question on acceptability and palatability, a summary of the responses will be provided. Proportions and 90% confidence intervals using the Wilson score method without Yates continuity correction will be computed for binary responses to items in the palatability and acceptability assessment. For non-binary variables, proportions in each category will be provided.

10 CLINICAL PHARMACOLOGY PLAN

10.1 Pharmacology Objectives

The clinical pharmacology evaluations for this study are designed to inform the population pharmacokinetic modeling and simulation for pretomanid in children. These evaluations, including the specified PK sampling timepoints, are informed by and aligned with the PIP.

Primary

- Evaluate the pharmacokinetics of a single dose of pretomanid in children with RR-TB to identify the weight-banded doses of pretomanid to be evaluated in a future multiple dosing study in children

Exploratory

- Evaluate the contribution of dose, demographic and baseline characteristics, and HIV status and/or its treatment to the variability in pretomanid drug disposition, using population PK modeling

10.2 Pharmacology Outcome Measures

The PK assessments will be performed for all participants to determine plasma concentrations of pretomanid at selected time points. Bioanalysis of pretomanid will be performed centrally at the University of Cape Town Clinical Pharmacology Laboratory using a validated assay. From the plasma concentrations, the outcome measures in the following table will be derived. Primary outcome measures are listed below and will be addressed in a PK SAP; secondary outcome measures listed in Section 9.2 and will be addressed in the study's primary SAP. Together, these plans will define the content of the primary analysis report(s). These report(s) will form the basis for the primary study manuscript and results reporting to ClinicalTrials.gov.

Note: The numbering of the outcome measures in this section corresponds to the numbering of the objectives in Section 2.

10.2.1 Primary PK Outcome Measures	
10.2.1.1	• $AUC_{0-\infty}$ • CL/F (apparent clearance) • $AUC_{0-tlast}$ • AUC_{0-48} (area under the curve from time zero to 48 hours) • T_{max} (time of maximal concentration) • C_{max}
10.2.2 Secondary Outcome Measures	
10.2.2.1	• See Section 9.2.2.1
10.2.2.2	• See Section 9.2.2.2
10.2.3 Exploratory PK Outcome Measures	
10.2.3.1	• Associations between PK outcome measures as specified in Section 10.2.1.1, dose, demographic and baseline factors (e.g., age, weight), HIV status, and concomitant antiretrovirals (if applicable)

10.3 Pharmacology Study Design

The components of the pharmacology study design are the assignments of dose by weight, the PK sampling schedule, and the sample size (number of participants per group). These components were determined based on population PK modeling and simulation. The doses are selected to yield exposures similar to the typical value of 50.9 µg*hr/mL (AUC_{0-24} at steady state) observed in adults at the recommended dose (200 mg QD). The PK sampling schedule and the sample size are selected to yield acceptably precise parameter estimates in the population PK model as represented in the accuracy of dose identification.

Dosing by body surface area has not been considered. A theoretical foundation has been established for the influence of body weight and age (for young children) on clearance (37), the key parameter in the determination of dose. Modeling of the PK data from this study will first be based on these principles. If such modeling yields unsatisfactory results, body surface area may at that point be considered.

10.3.1 Background and Methodology

10.3.1.1 Pharmacokinetic Model

A population PK model for pretomanid was used to guide the decisions discussed here. The model was developed based on adult data from the Nix-TB study (Sections 1.2.5 and 1.2.6) and the bioavailability study CL-011 (Section 1.2.4), describing variability across the two formulations (a child-friendly dispersible tablet and the marketed formulation) at varied doses (10, 50, and 200 mg) and two populations (healthy volunteers and TB patients). In Nix-TB and for the data used for modeling from CL-011, pretomanid was administered with food. The structure of the model was one-compartment disposition with first-order elimination and first-order absorption with delay. The PK parameters of the model were the mean transit time (MTT) to describe the absorption delay, the absorption rate constant (k_a), the relative bioavailability (F), the clearance (CL), and the volume of distribution (V_d). Allometric scaling was applied to typical values of CL and V_d with coefficients of 0.75 and 1, respectively. The typical bioavailability F was proportional to the dose and was expressed by a power function: $F = (Dose/200)^{0.081}$. Thus, for example, bioavailability was 11% and 22% lower at 50 mg and 10 mg compared to the 200 mg doses of pretomanid. Additional parameters of the population PK model characterized between- or within-subject variability of the PK parameters, as well as noise in measured concentrations. Sex was found not to be a significant covariate in the model, so the inclusion of only participants assigned female sex at birth in this study will not be limiting.

To scale adult information to children, a function characterizing the maturation of metabolizing enzymes in the youngest children was added to the PK model described above. Pretomanid is eliminated by metabolism through a complex set of pathways for which only a 20% contribution of CYP3A4 has been explicitly quantified. Thus, in the model, 20% of the maturation was attributed to a reported function for CYP3A4 (38), and the remaining 80% was assumed to follow a moderate rate of maturation according to a reported function for paracetamol.(37, 39) These components together generate a fraction between 0 and 1 as a function of age that multiplies the typical CL in the model. All simulations and estimations were performed using NONMEM 7.4.4.(40)

10.3.1.2 Simulation Population

To propose doses for the study and to evaluate the sampling schedule and sample size, a population of simulated patients with TB was generated with age uniformly distributed between 0 and 18 years old. Sex was simulated with a 50/50 probability. Given age and sex, individual body weights were calculated through a TB-adjusted LMS method based on growth curves from WHO and NHANES.(41, 42) A population including 30,000 simulated patients was sampled from participants with body weights above 4 kg. Given the age and weight, a participant's PK parameters were sampled from the distributions determined by the population PK model's typical values and between- and within-subject variabilities. A simulated patient is a set of values for age, weight, and the PK parameters, MTT, k_a, CL, V_d, and, at a particular dose, F.

10.3.1.3 Dosing Table

The goal of dose selection for this study was to find doses that would yield, for children with different weights, exposures, as measured by $AUC_{0-\infty}$ after a single dose, close to 50.9 μg*hr/mL, the median value of steady-state AUC_{0-24} observed in the Nix-TB study (the two metrics are regarded as identical as individual clearance of pretomanid remains constant). For an individual with clearance CL and with bioavailability F at a dose D, such an AUC is equal to F*D/CL. Thus,

for each simulated patient, AUC could be calculated for any dose and compared to the target value.

In principle, an individually optimal dose could be selected for any real patient in this way. However, there are practical limitations. Firstly, the patient's values of CL and F would need to be known, which is never the case in the real world, unlike the virtual world of simulations. Secondly, not all doses of pretomanid are available. There are only two strengths of the dispersible tablet formulation, 10 mg and 50 mg, although each is scored. Thus, only doses that are multiples of 5 mg are possible. Thirdly, to allow all possible multiple-of-5-mg doses would result in a complex dosing table that would be inconvenient for widespread use.

Therefore, it was decided to partition the pediatric patient population into a small number of weight bands and for each band to select one dose that would generate a median exposure near and not below the target within each weight band. After some preliminary investigations of weight distribution in previously conducted trials among pediatric TB patients and internal discussions with clinicians familiar with the patient population, the weight bands as indicated in Table 5 were selected.

10.3.1.4PK Sampling Times

A sampling schedule as indicated in Table 8 with six samples was proposed empirically. Alternatives with earlier or later last sampling time point (24 hr, 5 samples by removing the 48 hr, and 72 hr, 7 samples by adding after 48 hr) and a richer schedule (0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48 hr) were also investigated. While both sampling times and sample size (number of individuals) affect the accuracy of model-based inferences, the sampling times were primarily investigated with the sample size fixed to 36 (nine participants per group), as proposed in the PIP, to select the time points that would provide acceptable accuracy while being practically feasible and minimizing the burden on the participants. The sample size was then evaluated given the selected sampling schedule, as discussed below.

Scenarios with different PK sampling schedules were simulated. The population PK model was used to simulate 500 replicated trials, each of which included 36 participants randomly sampled from the simulated population. The same participants were used for all the scenarios to avoid noise generated by using different random samples. The simulation was followed by re-estimation using the same PK model given each PK data set. Re-estimations were performed of all PK parameters except the parameters of CYP3A4 maturation. The accuracy in CL/F (determining AUC) per median weight and the corresponding age in each weight group was the key evaluation metric and was represented by a 90% confidence interval around the geometric mean estimate. The schedule with the least number of samples and shortest sampling period that generated accuracy in CL/F in line with the most extensive sampling schedule option was selected.

10.3.1.5Sample Size

The evaluation of the sample size was based on the resulting accuracy of model parameter estimates as measured by the accuracy in identifying optimal doses.

As discussed above, the population PK model is defined by its structure (one-compartment, etc.) and by parameters, such as the PK parameters, the variability parameters, and the maturation parameters. The PK and variability parameters come from the previous model-development step, using data from Nix-TB and CL-011. The maturation parameters were assumed based on a mix of

prior knowledge about pretomanid and general knowledge of many drugs. All the simulations for the design of this study have used those assumed parameter values as if they were true. However, the main objective of this study is to re-estimate those parameters based on data from this study, and then to use those re-estimated parameters for revising, if necessary, dose selection for the next, multiple-dose study.

The logic of the assessment of sample size is as follows:

1. Assume the current parameter values are true.
2. Based on these parameters, identify an optimal dose for each weight band, using a criterion described below. Call the result the "true" optimal doses.
3. Simulate many replicates of this trial using the population PK model with the current (assumed true) parameter values.
4. With the data from each simulated replicate, estimate the model's parameters, and with those estimated parameters, identify an optimal dose for each weight band using the same criterion as in step 2.
5. Compare the estimated optimal doses based on the simulated trials with the "true" optimal doses from step 2.
6. If the estimated optimal doses tend to be close to, specifically within 60%–140% of, the "true" optimal doses, then the model's parameters are judged as being estimated with good accuracy.

Implementation of that logic made use of the simulated population described above. The simulated 30,000 patients of the simulated population were assigned to the corresponding dosing groups by weight according to the dosing table. Based on true parameters of all individuals within a dosing group, an optimal group dose (***GD****) was selected to provide $AUC_{0-\infty}$ closest to the target value, by minimizing the root mean squared error (RMSE) as defined below. The available doses to be selected were multiples of 5 mg from 5 mg to 200 mg.

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n=Ngrp_m} [\log(AUC_{dose,i}) - \log(AUC_{target})]^2}{n}}$$

$Ngrp_m$: Number of participants in the m^{th} dosing group
$AUC_{dose,i}$: The AUC of i^{th} participant at a given dose
AUC_{Target} : 50.9 µg*hr/mL

The proposed sampling schedule and sample size of 36 were used to simulate 500 *in silico* replicates of this trial. In each simulated trial, patients were randomly sampled from the simulated population, and PK observations were simulated for each sampled simulated patient as if that patient received their corresponding ***GD****. The population PK model's parameters were re-estimated given the simulated PK data, producing 500 re-estimated sets of model parameters and, based on those parameters, 500 sets of estimated optimal doses $GD^{\#}$. The ratio of the $GD^{\#}$ to the ***GD**** was calculated for each dosing group and each study age group.

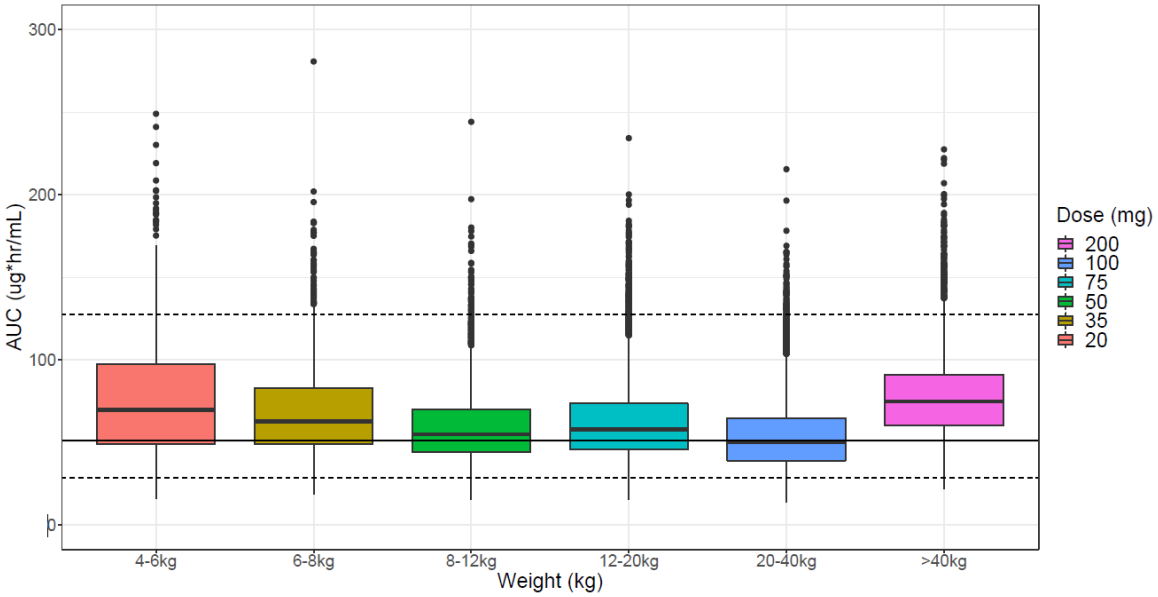
The power of the study design was summarized for each dosing group and each study age group as the percentage of the 500 ratios within specified limit of 60–140%. The sample size was judged adequate for ensuring accuracy of the PK model's parameter estimates if the power was at least 80%.

It may be noted that the "optimal" doses used for the evaluation of the sample size differ for some weight bands from the doses being used in this study. The "optimal" doses are defined to yield exposures that on average are as close as possible to the target. Such a notion is useful in that it makes for a workable mathematical algorithm to evaluate the accuracy of parameter estimation in terms of dose identification. But then about half of exposures at such a dose may be less than the target. Considering doses for the study, clinical judgment may allow nudging some doses higher to assure more target attainment while still maintaining safety. Meanwhile, higher doses are generally also useful for obtaining more information about drug disposition. Such judgment was applied to the choice of doses in this study as described in Section 10.3.2 to consider more practical reasons.

10.3.2 Dose Selection

The population was subdivided into six groups to enable different doses for different weights. The simulations indicated that the suggested doses (Table 5) would yield exposures similar to the target exposure derived from adults (Figure 2). The highest dose of 200 mg was chosen for the group greater than 40 kg to align with the adult dose. A dose of 20 mg is expected to be suitable for the lightest children under 6 kg with a maturation function similar to that of paracetamol clearance.

Figure 2. Boxplot of Pretomanid Exposures Given Selected Doses versus Dosing Groups



Solid lines represent the observed median (50.9 µg*hr/mL) in adults. Dashed lines represent the 90% prediction intervals of adult exposures.

10.3.3 PK Sampling Schedule

The parameter accuracy of different sampling schedules was visualized for the median weight and age in each dosing group (Figure 3). The initially proposed schedule with two-day duration (48 hr, control) performed similarly compared with a three-day (72 hr) schedule, while a one-day study (24 hr) notably decreased the precision and biased the estimation downward. Doubling the number of sampling time points within 48 hours did not improve the accuracy markedly.

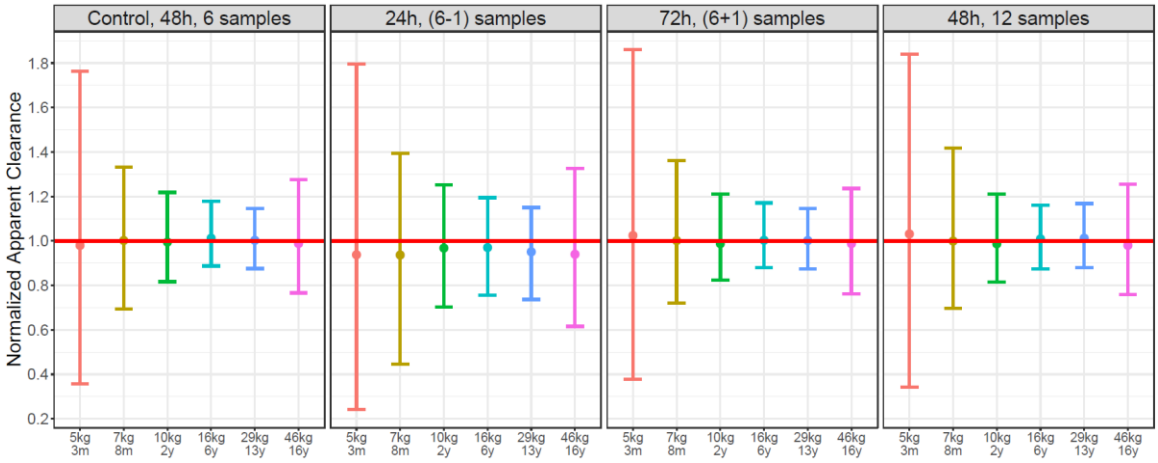
Table 12 shows the median prediction error (PE) per parameter related to clearance (determining overall exposure). In the 24-hour scenario, all the parameters were more biased as compared to the other scenarios. It could also be noticed that the 72-hour and richer schedules generally provided slightly better median PE than the proposed schedule. However, the improvement was minor. Hence, aiming at a smaller number of samples and shorter study duration, the proposed schedule with six samples over 48 hours was found to be robust enough among the tested alternatives, and was carried forward to the evaluation of study design.

Table 12. Median Prediction Error (PE) for Apparent Clearance-related Parameters in Each Scenario

Scenario	TVCL	CL~WT	F~Dose	Hill	TM50
Control, 48 hr, 6 samples	-0.53%	-3.22%	26.48%	34.23%	13.79%
24hr, (6-1) samples	-7.03%	-12.52%	-49.73%	125.24%	18.32%
72hr, (6-1) samples	-0.47%	-1.77%	39.59%	31.67%	8.85%
48hr, 12 samples	-0.69%	-1.46%	42.42%	37.68%	8.10%

"Control" refers to the initially proposed schedule; "24-72hr" represent the last sampling time point at each scenario; "n samples" represents the number of samples taken at each scenario.
Abbreviations: TVCL, typical value of Clearance; CL~WT, allometric scaling factor for body weight on CL; F~Dose, Dose effect on bioavailability; Hill, hill factor of maturation function; TM50, time to half maturity.

Figure 3. Accuracy of Apparent Clearance with Different Sampling Schedules

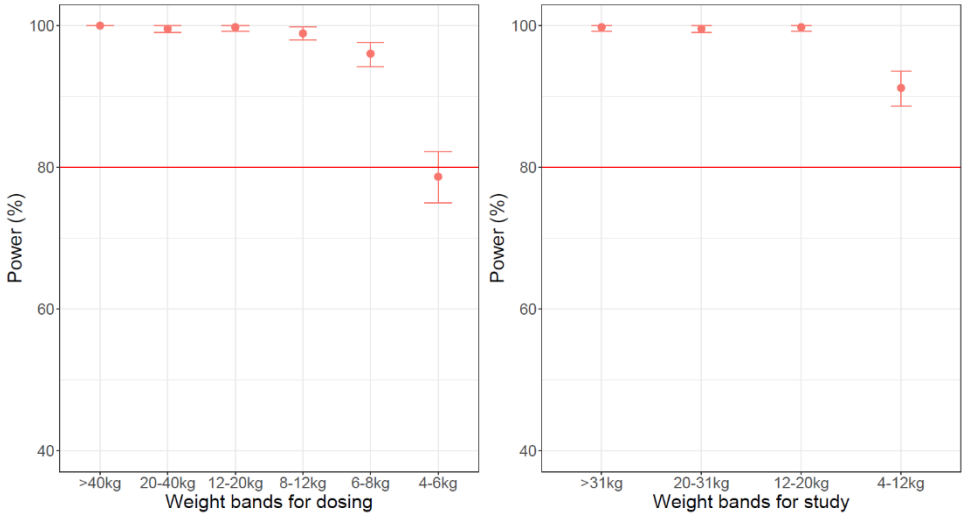


The median apparent clearance (dot) at each weight and age with 90% confidence interval (error bar, 2.5% and 97.5% percentiles) was normalized with the corresponding true value.

10.3.4 Sample Size

The power of a sample size of 36 with the proposed sampling schedule is shown in Figure 4. All dosing groups achieved more than 90% power to meet the accuracy criterion of 60%–140%, for dose selection while the lightest group was slightly below 80%. All study groups achieved more than 85% power with nine participants in each group.

Figure 4. Power of Sample Size of 36 for Different Dosing Groups and Different Study Groups



Error bars represent the 95% confidence interval of the power value given 500 simulations. Red line represents a reference power of 80%.

To conclude, it is sufficient to subdivide the population into six weight groups with doses ranging from 20 to 200 mg. The sample size of nine participants per group generally fulfills the preset criterion as suggested by FDA for pediatric study design, through evaluating the accuracy of dose identification in each dosing group and study group.

10.4 Interim Analysis

An interim analysis will be conducted after at least 12 PK-evaluable participants have been enrolled in Groups 1 and 2 combined and at least 12 PK-evaluable participants in Groups 3 and 4 combined. The simulation study described in Section 10.3.1.5 will be repeated based on a population PK model fitted to the newly available pediatric data, and the sample size will be re-evaluated. As noted in Sections 9.5.1 and 9.5.2, both the CMC and SMC will review the results from the interim analysis.

The timing and sample size of the interim analysis is based on a trade-off between having enough information to make a meaningful update of the population PK model (as late as possible is optimal) and avoiding an extension in the overall accrual period (and thus delay in study data availability) if the overall study sample size needs to be increased (as early as possible is optimal). Conducting the interim analysis with at least 24 participants balanced over weight groups allows estimation of the population PK model and enables sample shipment, bioanalysis, data analysis, and decision making to occur concurrently with continued participant accrual, with a goal towards seamless continuation of enrollment if the sample size needs to be increased.

If 36 evaluable participants with nine per group are found to be adequate, based on the original analysis (Section 10.3), then enrollment will continue until those targets have been reached. Otherwise, new targets, possibly up to 72 participants in total with 18 per group, may be set.

10.5 Pharmacokinetic Analyses

10.5.1 Noncompartmental PK Analysis

For each participant, the following PK parameters will be computed by standard noncompartmental methods: T_{max}, C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}48}$. Noncompartmental analysis will only be performed at the end of the study when all data are available.

The PK parameters will be summarized by group, by dose, and overall, with the following summary statistics:

- Sample size
- Arithmetic mean
- Standard Deviation (provided n > 2)
- Geometric Mean: Antilog of the arithmetic mean of the log-transformed values
- Geometric coefficient of variation: $[\exp(\sigma^2) - 1]^{½}$, where σ^2 is the variance of the log-transformed values (provided n > 2)
- Minimum
- Median
- Maximum

10.5.2 Population PK Analysis

The data will be analyzed by population PK modeling, first at the interim analysis and then after data from all participants are available. At the interim analysis, the parameters of the model will be estimated with the available data. The model with those newly estimated parameters will be used to evaluate the sample size according to the methodology described in Section 10.4. When all data are available, the parameters of the model will again be re-estimated and the ability of the model to describe the data evaluated. If the model fit is suboptimal, alternative structures, stochastic components, and covariate relations will be considered.

The final model will be used to derive individual parameters $AUC_{0\text{-}\infty}$ and CL/F. These parameters will be summarized in the same way as the parameters from the noncompartmental analysis (Section 10.5.1). Furthermore, the final model will guide dose selection, sample size, and PK sampling times for the follow-on, multiple-dose, PK, safety, and efficacy study ("PAEDIATRIC-2" or "Study 5" in the PIP). The methodology will be similar to that used to select the doses, sampling times, and sample sizes for this study, as described above. Details of the PK analysis will be available in a PK Statistical Analysis Plan (PK SAP).

10.5.3 Exploratory PK Analysis

The association between age, weight, and HIV-status and pretomanid pharmacokinetics will be explored in the population PK model. Age will be evaluated for impact on clearance (maturation) and bioavailability; weight and HIV-status will be evaluated on all disposition parameters and HIV-status also on bioavailability. Additional demographic and baseline characteristics, as well as HIV treatment, may also be considered.

11 DATA HANDLING AND RECORD KEEPING

11.1 Data Management Responsibilities

As described in Section 4.5, data on screening and enrollment in this study will be collected using the DMC SES.

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled participants, including paper-based CRFs (if used), eCRFs, and supporting source data. In maintaining these records, sites must comply with the standards of source documentation specified in the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual, which is available at:

https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

eCRFs and an eCRF completion guide will be made available to study sites by the DMC. Study staff will enter required data into eCRFs, with system checks applied and data queries generated immediately upon saving the entered data. Data must be entered within timeframes specified by the DMC; queries must also be resolved in a timely manner. Selected laboratory data will be transferred electronically to the DMC through the LDMS or through other secure mechanisms.

The Protocol Team and/or study oversight bodies (e.g., SMC) may determine that additional source data associated with procedures or evaluations performed per protocol should be entered into eCRFs so that the data can be used for analysis or to otherwise assist with interpretation of study findings. In such cases, sites will be officially instructed to enter the additional data into eCRFs from available source documentation.

Further information on eCRFs and IMPAACT data management procedures will be provided by the DMC. A User Manual for the Study Enrollment System is available on the DMC portal at:

https://www.frontierscience.org

11.2 Essential and Source Documents and Access to Source Data

Study sites must comply with DAIDS requirements for essential documents and source documentation as specified in the SCORE Manual. This includes establishing SOPs for maintaining essential and source documents. Site SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study, and site SOPs should be followed throughout the study.

Per the DAIDS policy on Storage and Retention of Clinical Research Records, study records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility during the conduct of the study and after the study is completed. Records must be retained for a minimum of three years after the completion of the study. Per 21 CFR 312.62, records must be maintained for two years after the date a marketing application is approved for one or more of the study products for the indication for which it is evaluated in this study; or, if no application is filed, or if the application is not approved for this indication, records must be retained two years after the study is discontinued and the FDA is notified.

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, IMPAACT, the Global Alliance for TB Drug Development (TB Alliance), the US FDA site drug regulatory authorities, site IRBs/ECs, the Office for Human Research Protection (OHRP), and other US, local, and international regulatory entities. Records must be kept on-site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID or NICHD. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID or NICHD.

11.3 Quality Control and Quality Assurance

Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the DAIDS SCORE Manual.

12 CLINICAL SITE MONITORING

Under contract to NIAID or NICHD, site monitors will inspect study site facilities and review participant study records — including informed consent and assent forms, paper-based CRFs (if used), eCRFs, medical records, laboratory records, and pharmacy records — to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. Monitors also will review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by monitors.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID or NICHD. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to ensure the safety of study participants and data integrity.(43) Site investigators will make available study documents for site monitors to review utilizing a secure platform that is 21 CFR Part 11 compliant. Potential platform options include: Veeva SiteVault, Medidata Rave Imaging Solution, Medidata Remote Source Review, site-controlled SharePoint or cloud-based portal, and direct access to electronic medical records. Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by DAIDS Office of Clinical Site Oversight (OCSO) or NICHD.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Board/Ethics Committee Review and Approval

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific informed consent and assent forms in accordance with 45 CFR 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must promptly report to the IRBs/ECs any changes in the study and must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b) for promptly reporting the following: unanticipated problems involving risks to participants or others; serious or continuing noncompliance with applicable regulations or the requirements or determinations of their IRBs/ECs; and any suspension or termination of IRB approval.

Sites are frequently overseen by more than one IRB/EC. Site investigators are responsible for awareness of and adherence to the policies and procedures of all applicable IRBs/ECs. All such policies and procedures must be followed and complete documentation of all correspondence to and from all applicable IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Manual (see also Section 14.2).

13.2 Vulnerable Participants

It is NIH policy to ensure that children be included in clinical research when appropriate (44). This study responds to that mandate and will provide clinical research data to inform pretomanid safety and dosing for children with RR-TB. Nonetheless, the children who take part in this study are considered vulnerable participants per the US Code of Federal Regulations (CFR), and IRBs/ECs must consider the potential risks and benefits to child participants as described in 45 CFR 46 Subpart D. Site IRBs/ECs must consider the potential benefits, risks, and discomforts of the study for children and assess the justification for their inclusion in this study. As part of this assessment, IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process described in Section 14.2, and the risk category assigned by the IRB/EC determines the parental informed consent requirements for the study at each site. Per 45 CFR 46.408 (b), the IRB/EC may find that the consent of one parent is sufficient for research to be conducted under 46.404 or 46.405. If the IRB/EC finds that the research is covered by 46.406 or 46.407, both parents must give their consent, unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child (as determined locally). IRBs/ECs must document their risk determination, and study sites should adapt the signature pages of their site-specific informed consent forms (ICFs) as needed to accommodate the parental consent requirements associated with the IRB/EC determination.

Study sites must comply with the requirements for enrolling minors in clinical research as specified in the DAIDS SCORE Manual. In accordance with these requirements, sites must establish and maintain written procedures describing local standards for identifying who may serve as guardian for a clinical research participant and how guardianship will be recognized. Guardianship will be documented at study entry, including whether the participant's guardian is a parent, other family member or individual, or governmental or non-governmental organization or institution. Should any changes of guardianship occur during study participation, these will be similarly documented. The site investigator must notify the CMC of any change of guardianship and must obtain informed consent from the new guardian for continued study participation.

In addition, to the US regulations cited above, sites must also comply with all applicable local and national and international guidelines and regulations. In cases where multiple different sets of requirements apply, the most stringent requirements must be followed.

13.3 Informed Consent and Assent

Refer to Section 4.5 for further information on informed consent procedures for this study. Refer to Appendix II and Appendix III for sample informed consent and assent forms.

If the potential participant is not of legal age to provide independent informed consent: Written informed consent for study participation will be obtained from each potential participant's parent or legal guardian before any study-specific procedures are performed. It is generally expected that the consent of one parent (or legal guardian) will be sufficient for child participation in this study. However, consenting requirements at each site will depend on the IRB/EC risk determination as described in Section 13.2.

When applicable per IRB/EC policies and procedures, written assent will also be obtained from the potential participant before any study-specific procedures are performed. If the parent/guardian does not provide consent, or the potential participant does not provide assent when applicable, the potential participant will not be screened or enrolled. Minor participants who assent to the study and later withdraw that assent will not be maintained in the study against their will, even if their parent/guardian still wants them to participate.

If the potential participant is of legal age to provide independent informed consent or, if applicable per local regulations, is considered a minor who is legally able to provide informed consent: Written informed consent for study participation will be obtained from each potential participant before any study-specific procedures are performed.

Given the short study duration, it is not expected that IRB/EC consent or assent requirements based on each participant's age at screening will change between screening and study completion at Week 2; sites should carefully consider screening and enrollment timeframes in relation to participants' age and consent/assent requirements.

The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. The process will include a description of what is currently known about the safety and efficacy of the study drug and the context of current local standards of care for RR-TB care and treatment. The assent process will include a similar but age-appropriate discussion. The amount of information and level of detail provided as part of the assent process should be tailored to the age and maturity of the potential participant, guided by applicable IRB/EC policies and procedures, including consideration of any legal rights for children to independently consent to HIV testing and reproductive and sexual health care. The extent to which HIV status or pregnancy test results are disclosed as part of the assent process should also be guided by applicable IRB/EC policies and procedures. Sites may develop multiple assent forms, if desired, in anticipation of different information needs across the study age range. When preparing site-specific assent forms, sites may remove or modify the wording included in the sample assent form to provide the most appropriate information and level of detail, consistent with applicable IRB/EC policies and procedures.

Should the consenting parent/guardian of an enrolled participant die or no longer be available for any reason, or should guardianship otherwise change for any reason, all applicable IRB/EC policies and procedures should be followed. Study-specific evaluations (outside the standard of care) should not be performed until informed consent for continued study participation is obtained from the participant's new guardian. If a new guardian cannot be identified, or if the

new guardian does not consent to continued study participation, the child must be withdrawn from the study.

In accordance with DAIDS requirements for enrolling children in clinical research, as specified in the DAIDS SCORE Manual, all sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled child, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

13.4 Potential Benefits

Participants in this study may experience no direct benefit. Participants and others may benefit in the future from information learned from this study, particularly information that may lead to more treatment options for children and adolescents with drug-resistant tuberculosis. Participants may also appreciate the opportunity for themselves to contribute to drug-resistant tuberculosis-related research.

13.5 Potential Risks

The potential risks of participation in this study include risks associated with study procedures and risks associated with receipt of a single dose of pretomanid.

Most study procedures are routine medical procedures that are associated with minimal to no risk. It is acknowledged, however, that the frequency at which some procedures will be performed for this study is not routine in clinical practice. The increased frequency of blood collection may be of potential risk, as blood collection may cause pain, bruising, swelling, or fainting. There is a very small chance of infection where the needle is inserted.

Refer to Section 1 and the IB for pretomanid for a description of the potential risks associated with the use of this drug.

Refer to Section 13.7 for further information on privacy and confidentiality. Despite efforts to maintain confidentiality, involvement in this study could become known to others, possibly leading to unfair treatment, discrimination, or other social impacts (e.g., because participants could become known as having TB or HIV). For example, participants could be treated unfairly or discriminated against or could have problems being accepted by their families and/or communities. Every effort will be made to protect participants' information, but this cannot be guaranteed.

13.6 Reimbursement/Compensation

Pending IRB/EC approval, participants will be reimbursed for costs associated with completing study visits (e.g., transport costs). Reimbursement amounts will be specified in site-specific ICFs and/or other materials per applicable IRB/EC policies and procedures.

13.7 Privacy and Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing as described in Section 11.2. Data or information from the study may be shared with drug companies who have agreements with IMPAACT and/or the NIH, or regulatory entities, but individual participants will not be identified.

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site (e.g., EAE report forms) will be identified by PID only. Likewise, communications between study staff and Protocol Team members regarding individual participants will identify participants by PID only.

Study sites are encouraged but not required by DAIDS to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

13.8 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases, including TB or HIV, identified among study participants to health authorities. Participants' parents or guardians will be made aware of all applicable reporting requirements as part of the study informed consent process.

13.9 Management of Incidental Findings

Site clinicians will inform participants and their parent/guardian of all clinically meaningful physical exam findings and laboratory test results, including results of ECGs and routine laboratory results (e.g., CBC and chemistry results). PK test results in this study will not be routinely provided. When applicable, site clinicians will provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

13.10 Management of New Information Pertinent to Study Participation

Study staff will provide participants or parents/guardians with any new information learned over the course of the study that may affect their willingness to remain in follow-up in the study.

13.11 Post-Trial Access to Study Drug

Post-study access to pretomanid is not relevant to participants in IMPAACT 2034 as this study is a single dose study, and participants will discontinue study drug prior to exiting the study.

14 ADMINISTRATIVE PROCEDURES

14.1 Regulatory Oversight

This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH), which are part of the United States National Institutes of Health (NIH). The TB Alliance will provide study drug for this study but is not involved in sponsorship or regulatory oversight of this study.

Within the NIAID, DAIDS is responsible for regulatory oversight of this study. DAIDS will distribute safety-related information pertaining to the study products prior to and during the conduct of the study, in accordance with its sponsor obligations.

NIAID and NICHD provide funding to the clinical research sites at which this study will be conducted. Each institute contracts with an independent clinical site monitoring group that will perform clinical site monitoring visits as described in Section 12. As part of this activity, monitors will inspect study-related documentation to ensure compliance with applicable US, local, and international regulatory requirements.

14.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the study informed consent and assent forms approved, as appropriate, by applicable IRBs/ECs, and any other applicable regulatory entities. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received.

Site-specific informed consent and assent forms will be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

For any future protocol amendments, upon receiving final IRB/EC and any other applicable regulatory entity approvals, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received. Site-specific ICFs will not be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which is available at:

https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual

14.3 Study Implementation

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable US, local, and international regulations. Study implementation will also be guided by the IMPAACT Network MOP, IMPAACT 2034 MOP, LPC, and other study implementation materials, which will be available on the study-specific website:

https://www.impaactnetwork.org/studies/impaact2034

Study implementation at each site will also be guided site-specific SOPs. The DAIDS SCORE Manual specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials (available on the website referenced in Section 11.2). These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

14.4 Protocol Deviation Reporting

Per the requirements for source documentation specified in the DAIDS SCORE Manual (available at the website referenced in Section 11.2), all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to applicable IRBs/ECs and other applicable review bodies in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported within IMPAACT, following procedures specified in the IMPAACT Network MOP.

14.5 ClinicalTrials.gov

The NIH Policy on Dissemination of NIH-funded Clinical Trial Information establishes the expectation that clinical trials funded in whole or in part by the NIH will be registered and have summary results information submitted to ClinicalTrials.gov for public posting. The Protocol Team will comply with this policy as well as the requirements of 42 CFR 11.

15 PUBLICATIONS

All presentations and publications of data collected in this study are governed by IMPAACT policies, which are available in the IMPAACT Network MOP.

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Appendix I: Schedule of Evaluations

Study Visit	Screening	Day 0	Day 1	Day 2	Week 2
Visit Window	*up to 28 days prior to Entry*	*Entry*	*24 hours post-dose ± 4 hours*	*48 hours post-dose ± 4 hours*	*Day 14 ±5 days*
CLINICAL EVALUATIONS					
Baseline medical and medication history	X	X			
Interval medical and medication history			X	X	X
Complete physical exam	X	X	X	X	X
ECG	X	Pre- and ~6-hrs post-dose			
Study drug administration		X			
Palatability and acceptability assessment[1]		X			
LABORATORY EVALUATIONS					
Diagnostic HIV testing[2] [if needed]	[6 mL]				
Pregnancy test[3] [if needed]	[X]				
CBC with differential and platelets[4]	1 mL	1 mL		1 mL	1 mL
Chemistries[4]	3 mL	3 mL		3 mL	3 mL
Intensive PK sampling[5]		4 mL	1 mL	1 mL	
Total Blood Volume	**4-11 mL**	**8 mL**	**1 mL**	**5 mL**	**4 mL**

1. Palatability and acceptability assessment should be conducted within approximately 30 minutes post-dose.
2. See Section 4.3.
3. At screening, participants who have reached menarche or who are engaging in sexual activity (self-reported) must have a pregnancy test, with results available prior to enrollment. Urine (5 mL) or blood (1 mL) tests are acceptable. The total blood volume shown above accommodates collection of 1 mL of blood, if needed.
4. CBC and chemistries are not required at the Day 0 (Entry) Visit if screening labs were drawn within 3 days. A smaller blood volume of 2 mL may be collected at indicated visits for chemistry evaluations for participants who are less than one year of age.
5. Intensive PK sampling will be done as indicated in Table 8 at Day 0 (1, 3, 6, 9 hours post-dose), Day 1 (24 hours post-dose), and Day 2 (48 hours post-dose). The blood volume per sample is 1 mL.

Appendix II: Sample Informed Consent Form for Study Participation
for the parent/legal guardian of children and for adolescents to assent

Version 1.0, dated 15 July 2022

<<Sites insert heading/identifying information as required by IRB/EC and institutional policies.>>

Sponsor / Study Title:	**National Institutes of Health (NIH) / National Institute of Allergy and Infectious Diseases (NIAID) / National Institute of Child Health and Human Development (NICHD) / National Institute of Mental Health (NIMH) / "Phase I Study of the Pharmacokinetics, Safety, and Acceptability of a Single Dose of Pretomanid Added to an Optimized Background Regimen in Children with Rifampicin-Resistant Tuberculosis"**
Protocol Number:	**IMPAACT 2034**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

If you are the parent or legal guardian of a child who may take part in this study, your permission will be needed.

Introduction

Your child is being asked to take part in the research study named above. For your child to take part, you must give your permission.

This form gives information about the study. Please read it or have it read to you. Ask any questions you may have. Take as much time as you need to understand the study. We will ask you questions to see if we have explained the study clearly.

Here is a summary of important information about the study:

- The study is testing a medicine called pretomanid (Pa) in children. Pretomanid is a medicine used to treat adults with tuberculosis (TB) that is resistant to some common medicines.
- Pretomanid is approved for use in adults. This study is the first to look at pretomanid in children.
- Your child will receive one dose of pretomanid.
- Your child will be in the study for follow-up for two weeks total.
- Your child will have clinic visits with physical exams and blood draws for laboratory tests.
- We will ask you and your child questions about your child's health, the medicine being tested, and other medicines.
- The primary purpose of the study is to determine how much pretomanid is in children's blood. Another purpose is to look at whether pretomanid can be safely used without bad side effects.

- There are some possible risks for children in the study. One possible risk is that pretomanid could cause side effects for your child. The most severe side effects include liver problems and heart problems.
- This study will only enroll girls and children who were female at birth. This is because there were some bad effects in the testicles of male rats. This study will not enroll boys or children who were male at birth.
- There may be no benefits for children in the study. Understanding how pretomanid works in children may help develop new combinations of TB medicines for children.
- Your child's participation in this study is voluntary.
- Your decision about your child's participation in the study will have no effect on the medical care your child receives at this clinic. Your child's access to services, and the benefits and rights your child normally has, will not be affected.

More information is given in this form about the study, its risks, and its benefits. You should feel that you understand the study before deciding whether your child will participate. If you decide your child will participate, you will be asked to sign and date (or make your mark on) this form. You will be offered a copy to keep.

About the Study

This study is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *<<insert site name>>*. The person in charge of the study at the study site is the study doctor listed on the first page of this form.

The study is testing a medicine called pretomanid in children with TB that is resistant to other TB medicines. This is called drug-resistant TB. If your child's TB is resistant to some medicines, they will need stronger and longer treatment.

The study will include up to 72 children from Brazil, India, South Africa, Tanzania, and Thailand. Each child will be in the study for about two weeks.

The organization that is providing pretomanid, called Global Alliance for TB Drug Development (TB Alliance), is supporting part of this study. The United States National Institutes of Health (NIH) are sponsoring this study.

1. The study is being done to test pretomanid in children.

There are many different kinds of TB medicines. Children with drug-resistant TB usually take a combination of several medicines. There are not as many TB medicines for children and adolescents as for adults because many TB medicines have not yet been tested in children.

The study will test if pretomanid is safe or causes any bad side effects when given to children. The study will also look at the amount of pretomanid in blood. This is called an intensive pharmacokinetic (PK) evaluation. You can read more information on PK in this study below.

Pretomanid is a new medicine for TB. As of December 2021, it is approved for adults in combination with other TB medicines in 13 countries across the world. It has also been prequalified by the World Health Organization (WHO). This means that the WHO helps make sure that medicines are high quality, safe, and work well. There have been some adolescents who were included in adult studies. This is the first study of pretomanid that will include only children.

2. Only children who are eligible can take part in the study.

If you decide to have your child take part in the study, we will first do some tests to find out if they are eligible. More information about the tests is given below. If your child is eligible, they will be entered in the study. If your child is not eligible, they cannot be entered in the study.

3. It is your decision whether to have your child take part in the study.

Deciding to join the study is voluntary (your choice). You may choose to have your child join or not join. If you choose to have your child join, you can change your mind and your child can leave the study. Your choices will have no effect on the medical care they would normally receive. Your child's access to services, and the benefits and rights they normally have, will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. You can bring other people here to learn about the study with you.

Depending on your child's age, we may also ask your child to give their permission to be in the study. This is called assent. If your child decides to join the study, they can change their mind and leave the study at any time.

No matter what you decide about the study, it is important that your child receive care and treatment for TB. We will tell you about your child's options for obtaining care and treatment for their TB.

Alternatives to participation

Your child does not have to be in this study to receive treatment for their condition. Your child will keep receiving medical care and their medicines for TB from outside the study. Your child may also qualify for other studies. Please ask any questions you may have about these alternatives.

Finding out if your child is eligible for the study

4. We will ask questions, examine your child, and discuss the study requirements with you.

To find out if your child is eligible for the study, we will:

- Review your child's medical records.
- Ask about your child's health and medicines.
- Talk with you about the study requirements and if you and your child are able to meet the requirements.
- Give your child a physical examination.
- Check your child's heart using an electrocardiogram machine (ECG). This machine measures the electrical activity of the heart through pads placed on your child's chest. Your child will need to stay very still for a few minutes while we check their heart.
- Draw your child's blood (up to 11 mL or about 2 teaspoons) for tests. The tests will:
  - Check your child's blood and blood cells.
  - Check your child's liver, kidney, and other organs.

- Check your child for HIV. Your child can participate in this study whether they are living with HIV or not. There are certain HIV tests that are required for this study. If the required tests are not in your child's medical records, we will do the tests that are needed. If the tests show that your child has HIV, we will tell you and/or your child where to go for medical care and other services your child might need. *<<Sites modify this bullet to include locally appropriate language regarding consent for HIV testing and disclosure of results to parents or guardians>>*
- If it is possible for your child to become pregnant, we will collect blood or urine to check for pregnancy. Children may be tested if they have had their first period or if they are sexually active. The pregnancy test must show that your child is not pregnant to be in the study.

<<Sites modify the following paragraph to include locally appropriate language regarding disclosure of pregnancy results to parents or guardians>> We will talk over the pregnancy test result when it is available with your child in private without parents or guardians present. Your child must give us permission before we can share these results with you. If the test shows that your child is pregnant, we will give them information on where medical care and other services can be received. If your child becomes pregnant during the study, we will contact you or your child after the last study visit to find out the outcome of the pregnancy.

If your child enters the study and they are sexually active, they will need to agree to use one form of birth control while in the study. We will talk to your child about how to prevent pregnancy.

These procedures will take about 4 to 5 hours. *<<here and throughout this form, sites may modify the expected visit duration as needed>>*

5. We will tell you if your child is eligible.

We will give you the results of all procedures and explain the results to you. We will tell you about getting care and treatment and any other services your child may need. While waiting for the results and if they join the study, it is important for your child to keep taking their usual TB medicines.

If your child is not eligible for the study for any reason, we will tell you this. Your child will not be entered in the study. Your child can and should continue to receive medical care and treatment outside of the study. We will tell you more about getting this care and treatment and any other services your child may need.

If your child does not enter the study, we will still use some information collected about them (for example, age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study.

If your child is eligible for the study, they will be entered into the study.

Being in the Study

6. If your child is eligible, they will enter the study.

Your child will have study procedures on the first, second, and third days from entering the study. At these visits, we will:

- Review your child's medical records.
- Ask about your child's health and medicines.
- Give your child a physical examination.

- Draw your child's blood (4 mL or less than 1 teaspoon) for tests on the first day and the third day. The tests will check:
  - Your child's blood and blood cells.
  - Your child's liver, kidneys, and other organs.
- Draw your child's blood on the first, second, and third day to check the amount of pretomanid. You can read more about PK testing below.

On the first day only, we will also:
- Check your child's heart using an ECG before and 6 hours after they take pretomanid.
- Give your child food. (If your child is breastfeeding, we will ask you to give them breast milk.)
- Help your child take pretomanid.
- *<<Sites may remove assessment of gender identity if there are any significant concerns about participant safety or may insert locally appropriate language as needed; sites may also modify the explanation of gender identity to align with locally applicable gender options and descriptions. >>* If your child is 12 years of age or older, we will ask them about their gender identity. Gender identity is the internal sense people have of whether they identify as male, female, gender non-binary, or another gender identity. A person's gender identity may be different from their sex at assigned birth. This will be done in private, without a parent or guardian being present.

On the first day, your child will be in the clinic all day. Throughout the day these procedures will take about 2 to 3 hours. *<<sites: modify how much time this visit will take as needed>>*

7. We will look very closely at the amount of pretomanid in your child's blood.

This is called an intensive pharmacokinetic (PK) evaluation. This is to see how much pretomanid is in the blood and how long it stays.

On the first day of this visit, we will give your child one dose of pretomanid while at the study clinic. This is so that we can help your child take pretomanid and know the exact time they took pretomanid. There are two different ways to give pretomanid, depending on how much your child weighs:
- For bigger children and adolescents, we will give pretomanid as a tablet. The tablet needs to be swallowed whole – it cannot be broken or crushed. We will give your child water to take with the tablet.
- For smaller children and infants, we will give pretomanid as dispersible tablets. Dispersible tablets are mixed with water to make into a liquid to drink. We will also give your child more water to take after the mixed tablets.

We will ask you or your child how it was to take the medicine (for example, how the tablet tasted or how easy or difficult it was to swallow the tablet).

<<Sites modify this paragraph to appropriately describe how the intensive PK evaluation will be conducted, including procedures for overnight stays>> On the first day after your child takes pretomanid, we will draw about 1 mL (about ¼ teaspoon) of blood at four different times. This will be about 1 hour after your child takes pretomanid and again 3, 6, and 9 hours after. We will draw about 1 mL after about one day and again after about two days. We will draw about 6 mL total (a little bit more than 1 teaspoon). We will look at the amount of pretomanid in the blood at each of these times. We will help you remember this before and during the visit. You and your child may be able to stay at the clinic or hospital during this visit. We will explain the options for this to you.

<<Sites modify this wording as needed to describe local intensive PK procedures>> We will place a small plastic tube (like a "drip") in your child's arm to draw blood for the PK test. The tube is attached to a plastic needle. The tube and needle will stay in place until all the blood draws are done. We will not need to stick your child with a needle each time.

8. After the PK evaluation, your child will have one more visit about 2 weeks after they take pretomanid.

At this visit, we will:

- Review your child's medical records.
- Ask about your child's health and medicines.
- Give your child a physical examination.
- Draw your child's blood (4 mL or about 1 teaspoons) for tests. The tests will check:
  - Your child's blood and blood cells.
  - Your child's liver, kidneys, and other organs.

These procedures will take about 1 to 2 hours.

Your child may have more visits after this visit if they feel sick or if more tests are needed to check on their health.

9. The tests for the amount of pretomanid in your blood will be done at different laboratories.

We will do most tests of your child's blood or urine at our laboratory. We will give you the results of most of these tests at the next scheduled visit, or sooner if necessary. We will explain the results to you. When we look at your child's test results, we might see that they need medical care or treatment that we cannot give them. We will tell you where you can go for this care.

We will also draw blood to check the amount of pretomanid in your child's blood. The test will be done at laboratories in South Africa or other countries. We will not give you the results of this test during the study.

10. We may take your child off the study early.

We may take your child off the study if:

- Your child cannot or does not take pretomanid.
- The study is stopped for any reason.
- Your child is not able to come to the study visits or we determine that they cannot meet the study requirements.
- We determine that staying in the study might harm your child.

11. Please tell us if you want your child to leave the study.

You are free take your child off the study at any time for any reason. The care at this clinic will not be affected, but it is important that we know your decision. We will answer any questions you may have and tell you how to contact us in the future, if you wish.

If your child leaves the study early, we will still use the information and samples already collected from your child. However, if you do not agree to this, you can tell us and your decisions will be followed.

Risks of the Study

Taking part in this study may involve some risks and discomfort. Most procedures done in this study are routine medical procedures, with little risk to your child. However, some procedures will be done more often in the study than in regular medical care. People working on the study have been trained to minimize the risks of the procedures.

Study risks include:

- risks from study procedures
- risks from pretomanid
- risks to your child's privacy

12. There is little risk from study procedures.

Blood draws

Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

ECG

Small sticky patches are put on the chest to do the ECG to check the heart. ECG patches may cause a skin reaction such as redness or itching. A small amount of hair may also be removed with the placement of the ECG patches.

HIV testing

Your child may be tested for HIV while in this study. You or your child may become worried or anxious about their test results. We will explain all tests to you and provide counseling to help with feelings you or your child may have about the tests and their results.

13. There are risks from pretomanid.

All medicines to treat TB can cause side effects. This includes the medicines your child is taking outside the study. Some side effects are minor, and some can be severe. Some are common and some are rare. Some people who take pretomanid have some of these effects. Some people have different side effects.

Some of the most common and most serious effects are listed below. Healthy adults and adults with drug-resistant TB have taken pretomanid in other studies. There may also be unknown side effects because this is the first time pretomanid will be studied in children. The lists do not include all the possible side effects. If you have questions about side effects not included in these lists, you can ask us.

We will also check for any side effects during the visits and tell you what to do if your child has any side effects.

14. Some side effects can be mild.

The following effects have been seen in some of the people who took pretomanid in other studies. They are usually not severe. These are listed below. These can be more or less common.

- Headache
- Nausea (feeling sick)
- Vomiting (being sick)
- Rash
- Difficulty passing stool (constipation)
- Lightheadedness, fainting, or rapid heartbeat when standing up after lying down
- Changes in blood tests that may show problems with the liver (The liver is an organ near the stomach. It helps digest food and keep the body healthy.)

15. Some side effects can be severe.

The following severe effects have also been seen in some of the people who took pretomanid in other studies. These effects are rare but can cause serious health problems and can result in death. These side effects were seen when adults took pretomanid with other TB medicines for several months.

Please contact us right away or go to the nearest hospital if your child has any of these side effects.

Liver problems

Problems of the liver can be seen with abnormal blood test results. Some abnormal liver tests are explained by other health conditions such as an infection with a new virus, like Hepatitis A, B, or C. Liver problems can be worse when pretomanid is taken with other medicines that can cause liver problems. Liver problems can also be worse when pretomanid is taken for many days. When healthy adults took pretomanid for less than two weeks, there were no severe liver problems.

Blood tests to check the health of your child's liver will be done during the study. Your child's study doctor will tell you if actions are needed.

Children with liver problems may have yellowing of the skin or eyes; dark or tea colored urine; pale colored stools; upset stomach or vomiting; poor appetite; weight loss; pain, aching, or tenderness in the belly, especially on the right side below the ribs. Children may feel tired or weak or dizzy or have difficulty breathing. When these types of problems happen, they can lead to failure of the liver and can result in death. Contact us right away if your child has any signs of liver problems.

Heart problems

Pretomanid can cause a specific kind of change to the heart called an increased "QT interval." An increased QT interval might put your child at greater risk of having a serious problem with the heart. In very rare cases, this can lead to death. Heart problems can be worse when pretomanid is taken with other medicines that can cause heart problems. When only pretomanid is taken, there is only a small change in QT interval (less severe).

ECGs to check the health of your child's heart will be done during the study. Blood tests will also be done to make sure certain chemicals (called electrolytes) in your child's blood are normal, because low levels of these chemicals can increase the QT interval. Your child's study doctor will also talk with you about

the other medicines your child is on. This is to make sure your child is not taking other medicines that might cause heart problems. Your child's study doctor will tell you if other actions are needed.

Pancreas problems

The pancreas is an organ near the stomach that helps digest food. People with pancreas problems may have stomach pain or upset stomach or vomiting. When adults took only pretomanid, there were no severe pancreas problems. When adults took pretomanid with other TB medicines, there were some severe pancreas problems.

Pancreas problems can be seen with abnormal blood test results. Blood tests to check the health of your child's pancreas will be done during the study. Your child's study doctor will tell you if actions are needed.

Contact us right away if your child has any signs of pancreas problems.

16. There may be other possible risks.

Some studies looked for side effects in animals given pretomanid. In rats, there were bad effects on the testicles that made it more difficult for them to have babies. This happened when the rats were given pretomanid for longer and at higher doses. We did not see the same effects in monkeys and other animals. There are other studies now looking for these bad side effects in people. So far, these studies in people do not show any changes in blood tests that may show problems with the testicles. Also in these studies, some men have been able to have children. The full results are expected soon. No bad effects were seen in female animals. Because of these bad effects in male rats, this study will not enroll males.

As this is the first study of pretomanid in children, there may be other risks that are unknown.

17. There could be risks of disclosure of your child's information.

We will make every effort to keep your child's information private and confidential. Study records and samples will be kept in secure locations. All samples and most records will be labeled only with a code number. However, your child's name will be written on some records.

The information we collect about your child will be combined with information collected about all other children in the study. This will be done at an organization called a statistical and data management center. The IMPAACT Network statistical and data management center is in the United States. We will send your child's information to this center. The information will be sent securely, following applicable laws and policies. Your child's name and other information that could personally identify them will not be sent.

Despite our best efforts to keep your child's information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, your child could be treated badly or unfairly. Your child could feel stress or embarrassment.

Information collected for this study may be used for other research in the future without additional informed consent. For example, researchers may use information from this study to try to answer different questions about children with TB or HIV. Any future research done with the information from this study must be approved by the IMPAACT Network. If any future research is done, information about your child may be used. Your child's information will be labeled with a code number and the only link to the code

number and your child's name will be kept here at *[site name]*. Your child's name and other information that could personally identify your child will not be given to other researchers.

The study doctor may be required by law to report the result of some tests to the local health authority.

Benefits of the study

18. There may be no benefit from being in the study.

By joining the study, your child will be part of the search for a medicine that may be better for children who have drug-resistant TB. We do not expect that being in the study will benefit your child.

Your child will have health checks and information learned from this study may help other children with drug-resistant TB.

Other Information about the Study

19. There are no costs for being in the study.

There are no costs to you or your child for study visits, pretomanid, or procedures.

<<Sites may insert information about compensation/reimbursement here, e.g., You will be reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount).>>

20. Study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- *<<All sites insert local IRBs/ECs as applicable>>*
- *<<insert name of site drug regulatory authority>>*
- *<<insert name of other site regulatory entities>>*
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other US, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- Global Alliance for TB Drug Development (TB Alliance) (the organization that is providing pretomanid)

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your child's name or identify them personally.

A description of this study will be available on http://ClinicalTrials.gov. This Web site will not include information that can identify your child. At most, the Web site will include a summary of the results of the study. You can search this Web site at any time.

Your child's study information may be disclosed to other authorities if required by law. *<<Sites add more specific detail here as needed; example follows:>>* For example, we are required to report any significant risk of harm to your child or others.

<<For sites in South Africa, add relevant language regarding the Protection of Personal Information Act (POPIA); sites not in South Africa may include any other local or national requirements to help ensure protection of personal information; example follows:>> We will also follow all requirements relating to data sharing and privacy as required by South African law.

21. Samples from your child will be used for study testing only.

The samples collected from your child will only be used for the testing described in this form. The samples will not be used for other research now or in the future. The samples will not be sold or used for commercial profit. For example, the samples will not be used to make a new product that could be sold.

22. If your child gets sick or injured, contact us.

Your child's health is important to us. We will make every effort to protect your child's well-being and minimize risks. It is possible, however, that your child could have an illness or injury that is study-related. This means the illness or injury occurred as a direct result of being in the study.

<<Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.>> If a study-related illness or injury occurs, we will treat your child or tell you where they can get the treatment they need. The cost for this treatment may be charged to you or your health insurance. There is no program to pay money or give other forms of compensation for study-related illness or injury through *<<site name or>>* the United States National Institutes of Health.

Who to Contact

23. If you have questions, concerns, or problems at any time, use these contacts.

<<Sites insert appropriate contact information as helpful for participants and as required by IRB/EC and institutional policies>>

During the study, if your child experiences any medical problems, suffers a research-related injury, or you have questions, concerns, or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document. If your child seeks emergency care, or hospitalization is required, alert the treating physician that your child is participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your child's rights as a research participant, and/or concerns or complaints regarding this research study, contact:

<<Name, phone number, and other relevant contact details of IRB/EC contact person or other appropriate person or organization>>

Signatures

If you want your child to take part in this study, sign or make your mark below.

Before deciding whether your child will take part in this study, make sure you have read this form or had it read to you. Make sure all your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of your child if they decide to take part.

We will tell you about any new information from this study or other studies that may affect your willingness for your child to stay in the study. You can ask questions or request more information at any time.

You do not give up any rights by signing this form.

<<Insert signature blocks as required by site IRB/EC policies.>>

Name of Participant (print)	Signature of Participant	Date
Name of Parent/Legal Guardian (print)	Signature of Parent/Legal Guardian	Date
Name of Study Staff Conducting Consent Process Name (print)	Signature of Study Staff	Date
Name of Witness (as appropriate; print)	Signature of Witness	Date

ASSENT for Children Under Age of Majority

I have been told that my parent/legal guardian agreed for me to participate in this research study as a minor. I have read and understand the information in this informed consent document. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I voluntarily agree to participate in this study until I decide otherwise. I do not give up any of my legal rights by signing and dating this consent document. I will receive a copy of this signed and dated consent document.

Name of Participant (print)	Signature of Participant	Date

Appendix III: Sample Informed Assent Form for Study Participation
for children who cannot provide independent informed consent for study participation

Version 1.0, dated 15 July 2022

<<Sites insert heading/identifying information as required by IRB/EC and institutional policies.>>

Sponsor / Study Title:	**National Institutes of Health (NIH) / National Institute of Allergy and Infectious Diseases (NIAID) / National Institute of Child Health and Human Development (NICHD) / National Institute of Mental Health (NIMH) / "Phase I Study of the Pharmacokinetics, Safety, and Acceptability of a Single Dose of Pretomanid Added to an Optimized Background Regimen in Children with Rifampicin-Resistant Tuberculosis"**
Protocol Number:	**IMPAACT 2034**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

<<The amount of information and level of detail provided in site-specific assent forms should be tailored to the age and maturity of study participants, guided by applicable IRB/EC policies and procedures. Sites may develop multiple assent forms, if desired, in anticipation of different information needs across the study age range. When preparing site-specific assent forms, the wording included in this sample form may be modified or removed in order to provide the most appropriate information and level of detail for participants, consistent with IRB/EC policies and procedures.>>

Introduction

You are being asked to take part in a research study. For you to take part, you must give your permission. Your parent or guardian must also give their permission.

This form gives information about the study. Please read it or have it read to you. Ask any questions you may have. Take as much time as you need to understand the study. We will ask you questions to see if we have explained the study clearly.

Your rights

It is up to you and your parent or guardian to decide if you will take part in the study. You can say yes or no. If you say yes now, you can change your mind later. If you decide not to take part, tell the site investigator. Your decision will have no effect on the medical care you normally receive.

About the study

The study is testing a medicine called pretomanid (Pa) in children with tuberculosis (TB) that is resistant to other TB medicines. This is called drug-resistant TB. This means that some medicines stopped working. If your TB is drug-resistant, you will need stronger and longer treatment.

There are different TB medicines. Children with drug-resistant TB usually take many TB medicines. There are not as many TB medicines for children and adolescents as for adults. This is because many TB medicines have not yet been tested in children.

The study will test if pretomanid is safe or causes any bad effects to children. The study will also look at the amount of pretomanid in blood. The study will include up to 72 girls. Boys will not be able to join the study.

What happens in the study

We will first ask some questions, review your records, draw blood, and examine you (check your body) to see if you are eligible for the study. We will also do a test to check your heart by putting small, sticky patches on your chest.

<<Sites modify this wording as needed to describe procedures, privacy, and disclosures related HIV and pregnancy testing to align with local standards of care and local standard procedures>> Some of the tests done to see if you are eligible for the study include tests for HIV and pregnancy. We will tell you the results of these tests. We will ask you if you want your parent or guardian to be present when we tell you the results.

If you are eligible, you will be in the study for about two weeks. You will keep taking your other TB medicines. We will give you pretomanid once. Depending on how much you weigh, you may need to swallow a whole tablet. The other way we might give you the medicine is mixed with water to drink. We will tell you which one you will take. We will ask you how it was to take pretomanid, like how it tasted or how it was to swallow.

You will be in the clinic a lot over three days and have your blood drawn many times. This is to see how much pretomanid is in blood. You and your parent or guardian may be able to stay overnight at the clinic. We will explain the options for this to you.

On the first day, we will draw blood at five different times. This will happen before you take pretomanid and four more times after you take pretomanid. We will draw a little bit more blood after about one day and again after about two days. On the first day, we will repeat the test to check your heart two more times – one time before you take pretomanid and about six hours later.

<<Sites modify this wording as needed to describe local intensive PK procedures>> On the day of the first visit, we will place a small plastic tube (like a “drip”) in your arm. The tube is attached to a plastic needle. The tube will stay in your arm until all the blood draws are done. We use the tube so we do not have to stick you with a needle each time.

You will come back one more time after two weeks to see how you are feeling and draw blood.

Some tests check your health. These will be done right away after each visit. We will tell you and your parent or guardian the results. We will not tell you and your parent or guardian about the results to see how much pretomanid is in blood.

We will tell you as much information as you want about the study. Please ask any questions you may have. Please tell us if anything bothers you or scares you. We will do our best to explain the study and help you feel more comfortable.

What good and bad effects could happen

By taking part in the study, you will be helping to learn more about pretomanid for children with TB. This may not have any benefits (good effects) for you. However, information learned in the study may have good effects for other children with TB in the future.

The medicine could cause bad effects. All TB medicines can cause bad effects. This includes any TB medicines that you would receive outside the study. Some bad effects are not that bad; others can be really bad. Some bad effects happen to a lot of people, while others only happen to a few people. Some people who take TB medicines have some of the bad effects, and other people have no bad effects. At all of your visits, we will check whether the TB medicines you are taking may be causing bad side effects. We will also ask you to tell your parent or guardian any time you do not feel well. You and your parent or guardian should also tell us if you do not feel well. We may ask you to come here so we can check on you and try to help you feel better.

Having your blood drawn may hurt. The patches we put on your chest to check your heart may be itchy. *<<Sites may modify the following sentence to align with local requirements and policies for HIV disclosures.>>* You may feel worried or anxious when doing some of the tests, like for HIV, or when waiting for the results. You may feel nervous or embarrassed when answering questions for the study.

There could be other bad effects. For example, other people could find out that you are in the study or learn things about you. We will do all we can to keep this from happening. For example, most of the records we keep here for the study will be labeled with a code number (not your name). We will share information about you, including information that you tell us, with your parent or guardian. We will not share your information with other people unless you or your parent or guardian ask us to.

Who to contact

<<Sites insert appropriate contact information as helpful for participants and as required by IRB/EC and institutional policies>>

You and your parent or guardian can contact us at any time. Please talk to your parent or guardian and to us about any questions or problems you may have. If you have any problems or get hurt, please talk to your parent or guardian. They should contact the study doctor at the telephone number listed on the first page of this document. If you have questions, concerns, or problems at any time, use these contacts.

An institutional review board (IRB) is a group of people that help protect the rights of research participants. If you have any questions about your rights in this study, contact:

<<Name, phone number, and other relevant contact details of IRB/EC contact person or other appropriate person or organization>>

Signatures

Before deciding if you want to be in the study, make sure you have read this form or had it read to you. Make sure all your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you if you decide to be in the study.

We will tell you and your parent or guardian any new information that could change your mind about being in the study. You can ask questions or ask for more information at any time.

You do not give up any rights by signing and dating this form.

<<Sites insert initial and signature blocks as required by IRB/EC and institutional policies.>>

Name of Participant (print)	Signature of Participant	Date
Name of Parent/Legal Guardian (print)	Signature of Parent/Legal Guardian	Date
Name of Study Staff Conducting Consent Process Name (print)	Signature of Study Staff	Date
Name of Witness	Signature of Witness	Date