Approvals

ACTG A5312

Statistical Analysis Plan for Primary Analysis

Version 3.0

This is ACTG A5312 SAP Version 3.0 with names of authors, names of publication writing team members and analysis timeline redacted.

The Early Bactericidal Activity of High-Dose or Standard-Dose Isoniazid among Adult Participants with Isoniazid-Resistant or Drug-Sensitive Tuberculosis

Protocol Version 3.0

ClinicalTrials.gov Identifier: NCT01936831

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Table of Contents

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcomes measures of ACTG A5312 that will be included in the primary manuscripts, and which address the primary and secondary objectives of the study. The Primary SAP outlines the general statistical approaches that will be used in the analysis of the study. It has been developed to facilitate discussion of the statistical analysis components among the study team, and to provide agreement between the study team and statisticians regarding the statistical analyses to be performed and presented in the primary statistical analysis report. It also describes the results for the primary and secondary outcome measures that will be posted on ClinicalTrials.gov. Outlines of analyses for the other objectives will be presented in the SAP for Other Objectives. Detailed outlines of tables, figures, and coding descriptions that will be included in the Primary Analysis Report are included in the Analysis Implementation Plan (AIP).

An original component of the EBA study, which would have participants infected with TB with inhA mutations take one of three doses of INH (5, 10, or 15 mg/kg daily) and participants infected with DS-TB take standard-dose INH (5 mg/kg daily), was terminated early by the TB TSG on May 4, 2018. Protocol version 3.0 allows enrollment of participants infected with TB with katG mutations into the EBA part of the study (Step 2) and randomizes them to one of the two treatment groups (15 or 20 mg/kg daily INH). This statistical analysis plan is based on version 3.0. Analysis for the participants infected with TB with katG mutations taking 15 or 20 mg/kg daily will be conducted after approximately 20 eligible participants in this group complete the 7-day treatment period, and data become available.

The two final statistical reports will be used for submission of results to ClinicalTrials.gov. Results are required to be submitted within one year of the primary completion date (PCD), which is the date the last participant with katG mutations is examined for the purposes of data collection for the primary outcome measure.

1.2 Key Updates to the SAP

Version	Changes Made	Date finalized
1	Original Version	7/2/2018
1	Protocol amendment review (Version 3.0) by Sachiko Miyahara and Xin Sun	3/28/2019
2	Review after LOA #1. Updated the protocol overview to describe the LOA and CMs and personnel changes. The plans for analysis are unchanged.	1/21/2021
3	A new lab, BARC, did culture for TASK participants enrolled in protocol Version 3.0 and reported re-cultured results after additional decontamination. These results were not supposed to be reported (were not reported previously) and will be excluded from analysis. Under protocol Version 3.0 TTP is not done in duplicate for each sample so this has been clarified. Clarified that a separate statistical report will be prepared for participants enrolled under protocol Version 3.0. Added Ryan Wu to statistical team.	5/5/2022

2 Protocol Overview

2.1 Study Design (Protocol Version 3.0)

This is a two-stage, two-step, phase IIa, open-label, randomized clinical trial examining the bactericidal activity (EBA) of (1) isoniazid (INH) at three different doses among patients with drug-resistant tuberculosis (DR-TB) and (2) INH at standard dosing among patients with drug-sensitive TB (DS-TB). In addition, the association between the EBA among patients with DR-TB and pharmacokinetic (PK) parameters, such as area under the curve (AUC)/minimum inhibitory concentration (MIC) of INH, will be examined.

The study will be conducted in 2 stages. Stage 1 will be a pilot for determination of feasibility (accrual and speed) and sample size verification, and Stage 2 will be the main study. During Stage 2, participants with acid fast bacilli (AFB) smear-positive pulmonary TB with a Mycobacterium tuberculosis isolate with an inhA mutation, which generally confers low-level INH resistance, will be randomized to receive INH at 5, 10, or 15 mg/kg daily for 7 days (Group 1). Participants with an M. tuberculosis isolate with a katG mutation (with or without an inhA mutation), which is associated with high-level resistance, will be randomized 1:1 to receive either INH 15 mg/kg or 20 mg/kg daily for 7 days (Group 3). During Stage 1, participants with M. tuberculosis harboring neither inhA nor katG INH resistance mutations (Group 2) will not receive study treatment, but a maximum of 48 in this group will have a sputum sample collected for MIC determination. During Stage 2, Group 2 participants will be enrolled as a positive control group and receive INH at 5 mg/kg daily for 7 days. Among patients receiving study treatment, serial sputum samples, including quantitative cultures and liquid cultures, will be collected daily between pre-entry and Day 7 to determine EBA of the study treatment over the treatment period.

Each stage consists of two steps. The goal of Step 1 is to determine the MIC distribution of M. tuberculosis strains among participants with DR-TB or DS-TB. The goal of Step 2 is to examine the treatment effect of INH at different doses among participants with an inhA mutation (in both stages), a katG mutation (in Stage 2 only) or DS-TB (in Stage 2 only). In Step 1, a spot sputum sample will be collected from all eligible participants for acid fast bacilli (AFB) microscopy, for genotypic determination of INH resistance (inhA or katG mutations), and for phenotypic determination of INH MIC. In Step 2, eligible participants will be administered INH daily for 7 days and have serial overnight sputum sampling for estimation of participant-specific EBA (both quantitative and liquid cultures). Intensive PK samples for INH quantification, and blood and saliva samples for NAT2 determination, will also be collected in Step 2.

Participants who are screened for the study, but are not eligible to receive study treatment will be referred without delay for appropriate treatment. Those who are registered or randomized to receive treatment will be referred without delay to appropriate treatment after completing study treatment (no later than Day 10).

SAMPLE SIZE: Among participants eligible to participate in Step 1 only, accrual targets are 70, 64, and 64 participants from Groups 1, 2, and 3, respectively. These participants may be enrolled during Stages 1 or 2.

Among participants eligible to enroll in Step 1 and Step 2, accrual targets are as follows:

- Group 1: 48 evaluable participants (16 completing treatment in each dosing cohort) from Stage 1 and Stage 2 combined. During Stage 1, 15 Group 1 participants were enrolled (5 per dosing cohort) as of March 26, 2015. Stage 2 opened and an additional 33 Group 1 participants will be randomized (11 participants added to each cohort, for a total of 16 participants per cohort)
- Group 2: 16 evaluable participants will be followed as a fourth Step 2 cohort, enrolled during Stage 2.
- Group 3: No participants in Group 3 will enter Step 2 during original component (i.e. Protocol Version 2.0). Protocol Version 3.0 will enrolled 20 participants in Group 3 Step 2, randomized 1:1 to either INH 15 mg/kg (n=10) or INH 20 mg/kg (n=10) daily, plus vitamin B6 ≥25 mg daily for 7 days.

2.2 Major Protocol Revisions

Version 2.0 of the study protocol had two Letters of Amendments (LOA). One additional LOA was approved by the TB TSG Steering Committee in September 2016 to improve accrual. Version 3.0 of the protocol was finalized on March 15, 2018. The list below summarizes the main purposes of the LOAs and the changes in Version 2.0 from Version 1.0 and in Version 3.0 from Version 2.0.

- LOA#1 (dated May 4, 2013) – approved on September 17, 2015

  The main purpose was to modify the protocol to reflect the decision to conduct A5312 as a non-IND study.

- LOA #2 (dated January 16, 2015) – approved on September 17, 2015

  The main purpose was to relax the Step 2 entry criteria to improve recruitment. The changes included, 1) HIV-positive candidates with CD4+ cell count of ≥50 cells/mm^3 (instead the original cut off of 200 cells/mm^3) are eligible for the study, and 2) The exclusion of current treatment, or treatment within 30 days prior to entry, with antiretroviral therapy (ART) or expected to initiate ART within 8 days after Step 2 entry has been removed.

- Protocol Version 2.0 (dated August 18, 2015)

  The main changes were to increase the target accrual for Groups 1 and 2 during Step 1 (the target accrual for Groups 1 and 2 during Step 2 remains the same), to change the consent forms, to change the inclusion criteria for Group 3 to allow participants who have a katG mutation with or without an inhA mutation to enter study, and update protocol for the completion of Stage 1.

- LOA #1 after Protocol Version 2.0 (dated October 2016) – approved by the TB TSG Steering on September 28, 2016

  The main changes were to relax the exclusion criteria on usage of second-line anti-TB drugs and/or antibiotics intended for bacterial treatment prior to Step 1 screening (relaxed Section 4.4.2 and removed Section 4.4.3 of the protocol).

- Protocol Version 3.0 (dated August 21, 2018)

  The main purpose of this amendment was to add a treatment cohort for participants with *katG* mutation (Group 3) randomizing them 1:1 to receive either INH 15 mg/kg (n=10) or INH 20 mg/kg (n=10) daily, plus vitamin B6 ≥25 mg daily for 7 days. Accrual targets were increased for Group 3 to recruit eligible participants.

- LOA #1 for Protocol Version 3.0 (dated August 3, 2020)

  On March 18, 2020 the ACTG Network Leadership issued guidance designed to protect the health of ACTG study participants and the ACTG research community and support the best outcomes for our research program. For A5312 this guidance closed recruiting of new study participants but allowed those in screening at that date to be enrolled. The LOA was implemented to reopen the study to screening and accrual.

In addition to the LOAs, five Clarification Memos (CMs) were issued after protocol version 1.0 was released, one CM was issues after protocol version 2.0 was released, and two CMs were issued after protocol version 3.0 was released. The list below summarizes the main purpose of each CM.

- CM#1 (dated July 25, 2013)
  The main purpose was to clarify the sample size descriptions in Section 9.4 and 9.6.2.5.

- CM#2 (dated June 27, 2013)
  The main purpose was to remove language regarding non-inferiority testing from the protocol.

- CM#3 (dated November 13, 2013)
  The main purpose was to remove secondary objective 1.3.5 and the corresponding endpoint (9.2.2.5) and analysis (9.6.2.5).

- CM#4 (dated January 13, 2014)
  The main purpose was to clarify that Brooklyn Chest Hospital will participate in Stage 1 of the protocol.

- CM#5 (dated February 4, 2014)
  The main purpose was to update the biohazard containment section to include instructions on the transport of Mycobacterium tuberculosis material.

- CM#1 on Protocol Version 2.0 (dated February 4, 2014)
  The main purpose of this memo was to remove ethambutol (EMB) resistance testing from the study.

- CM #1 on Protocol Version 3.0 (dated December 12, 2019)
  The main purpose of this memo was to clarify the sample size under Version 3.0, a total of 40 Group 3 participants, 20 in Step 1 only and 20 in both Step 1 and Step 2. It also clarified that CD4 results from any network-approved lab with IQA certification was acceptable, including that used in inclusion criteria.

- CM #2 on Protocol Version 3.0 (dated February 25, 2020)

This purpose of this memo was to clarify that participants who received 7 days or less of second-line anti-TB drugs in the 14 days prior to Step 1 screening needed to have a washout period of at least 7 days prior to Step 2 pre-entry sputum collection.

This statistical analysis plan is based on protocol version 3.0.

2.3 Hypotheses

1. In the majority of participants infected with TB with inhA mutations, drug concentrations can be achieved that will result in an early bactericidal activity (EBA) measured as the daily fall of log10 colony-forming unit (CFU)/mL sputum over 7 days (EBA0-7(CFU)) that is at least 50% the EBA0-7(CFU) of standard-dose isoniazid (INH) when given to participants with drug-sensitive TB (DS-TB).

2. High-dose INH will be well-tolerated in a majority of participants.

3. Among participants infected with TB with katG mutations (Group 3), the distribution of minimum inhibitory concentrations (MICs) will be wide, but nevertheless, INH at a dose of 15 or 20 mg/kg daily will have measurable activity.

2.4 Primary Objectives

1. Estimate the 7-day EBA, based on CFU counts, of INH among participants infected with TB with inhA mutations taking one of three doses of INH (5, 10, or 15 mg/kg daily), and participants infected with DS-TB taking standard-dose INH (5 mg/kg daily).

2. Estimate the 7-day EBA, based on time-to-detection (TTD), of INH among participants infected with TB with inhA mutations taking one of three doses of INH (5, 10, or 15 mg/kg), participants infected with TB with katG mutations taking 15 or 20 mg/kg daily, and participants infected with DS-TB taking standard-dose INH (5 mg/kg daily).

3. Determine the association between the area under the curve (AUC)/MIC of INH and the EBA of INH among participants with smear-positive pulmonary TB.

4. Describe the safety and tolerability of doses of 5, 10, and 15 mg/kg of INH administered daily among participants with sputum smear-positive pulmonary TB.

2.5 Secondary Objectives

1. Determine the steady state pharmacokinetics (PK) of INH among participants with sputum smear-positive pulmonary TB taking 5, 10, or 15 mg/kg daily, taking into account INH acetylator status (N-acetyltransferase 2 [NAT2] genotype).

2. Determine and describe the distribution of MICs of M. tuberculosis isolates with genotypic evidence of low-level INH resistance (inhA mutations), high-level INH resistance (katG mutations), or neither of these mutations among participants with smear-positive pulmonary TB.

3. Estimate the proportion of participants infected with a TB strain that has an inhA mutation that will achieve a target AUC/MIC that is associated with clinically-relevant reductions in mycobacterial burden defined as at least 50% the EBA0-7 of standard-dose INH when given to participants with DS-TB, by dose.

4. Estimate linear or nonlinear model parameters based on EBA measured separately by CFU counts and time to detection (TTD) for INH among participants infected with TB with inhA mutations taking one of three doses of INH (5, 10, or 15 mg/kg daily), participants infected with TB with katG mutations taking 15 or 20 mg/kg daily (if CFU data are available), and participants infected with DS-TB taking standard-dose INH (5 mg/kg daily).

2.6 Exploratory Objectives

1. Evaluate the correlation between EBA0-7 (TTD) and EBA0-7(CFU) among participants with smear-positive pulmonary TB.

2. Evaluate the ability of a new PCR method that uses salivary samples to correctly characterize NAT2 genotype compared to standard NAT2 genotyping methods using blood samples and sequencing methodology.

3. Estimate the prevalence of quinolone, and aminoglycoside resistance among study participants with MDR-TB receiving study treatment.

3 Definitions

3.1 Analysis Population

Safety population: Safety analyses will be intent-to-treat and include all eligible participants who took at least one dose of study drugs.

Efficacy population: The primary analyses will use a per-protocol approach, limited to participants who provide CFU and TTD data at both study entry and Day 7. For the model based analysis, all randomized participants who had at least one CFU count or TTD will be included.

3.2 Endpoint Definitions

The following is the calculation of log 10 transformed CFU/mL sputum at each time point.

- log10 CFU/mL = $\log_{10}$[(average of CFU/mL_A and CFU/mL_B) x (dilution factor) x $10^{(Dilution)}$] where the dilution factor is set to 20. CFU/mL_A and CFU/mL_B are measured from the same sputum sample at a time point.

  Example: If CFU/mL_A = 150, CFU/mL_B = 185, and dilution = 4, then log10 CFU/mL = 7.53

When multiple TTD results were obtained for a specimen (per Protocol Version 2.0 but not Protocol Version 3.0), the folllowing is the calculation of total TTD.

- The final TTD is the mean of TTD_A and TTD_B. TTD_A and TTD_B are measured from the same

sputum sample at a time point. If one of the TTD is missing, the other TTD will be used as the final TTD. In a rare case of observing TTD = 42 days, the sites will determine if the value should be used as is or treated as missing.

The following are definitions from Section 9.2 of the protocol document.

- EBA0-7(CFU)= [baseline log10 CFU/mL sputum (mean of log10 CFU/mL at pre-entry and day 0) – log10 CFU/mL at day 7]/7. For a CFU/ml count of 0, the log10 CFU/mL will be set to 0
- EBA0-7(TTD)= [baseline TTD (mean of TTD at pre-entry and day 0) – TTD at day 7]/7
- EBA0-2(CFU)= [baseline log10 CFU/mL sputum (mean of log10 CFU/mL at pre-entry and day 0) – log10 CFU/mL at day 2]/2. For a CFU/ml count of 0, the log10 CFU/mL will be set to 0
- EBA0-2 (TTD)= [baseline TTD (mean of TTD at pre-entry and day 0) – TTD at day 2]/2.
- EBA2-7(CFU)= (log10 CFU/mL sputum at day 2 – log10 CFU/mL at day 7)/5. For a CFU/ml count of 0, the log10 CFU/mL will be set to 0
- EBA2-7 (TTD)= [TTD at day 2 – TTD at day 7]/5

For Group 3, TTP results from contaminated samples and from TTP from re-culture results after an additional decontamination step will be excluded from analysis.

4 Statistical Methods

4.1 General Considerations

Baseline characteristics will be summarized by cohorts (by Group and treatment arm) but with no statistical comparisons comparing cohorts.

Categorical data will be summarized using N (%), and continuous data using N, min, Q1, median, Q3, max, and mean (STD) (when appropriate). Nonlinear mixed model using SAS procedure NLMIXED will be used to estimate the decrease of log10 CFU counts per day for the ‘early’ and ‘terminal’ phase as well as the increase of TTD per day. If there is no clear bi-phase pattern, linear mixed model using SAS procedure MIXED will be used. For TTD, log10 transformation may be applied if appropriate. Any modifications to outcome measures after the team has seen data collected after entry will be considered as post hoc.

The primary endpoint analysis is defined in Section 4.3.1; however, the secondary modeling approach, which is described in Section 4.3.2, might be more appropriate in case of missing CFU or TTP outcomes at baseline and Day 7.

4.2 Visit Schedule and Analysis Windows

- Screening visit window = within 2 weeks (14 days) prior to Step 1 entry

- Pre-entry visit window = approximately 2 days prior to Step 2 entry
- Step 2 entry visit = Day 0 in Step 2
- On-Treatment evaluations: conducted between Day 1 and Day 7. Participants will be discharged on Day 8.
- Post-Treatment evaluations: completed in a period of plus or minus 3 days from Day 21.

Note: Participants who do not complete 7 days of study treatment or who cannot provide at least 1 mL for all required overnight sputum samples through Day 7 will be discontinued from the study, and replaced.

- Schedule of Events

Evaluation	Screening	Pre-entry	Entry: Registration/ Randomization	Study Treatment (Days)							Discharge	Final Visit	Premature Discontin-uation
			Step 2 Day 0	1	2	3	4	5	6	7	Day 8	Day 21 +/-3	
Documentation of HIV status	X												
Medical/Medication History			X										
Complete Physical Examination	X												
Targeted Physical Examination			X	X	X	X	X	X	X	X	X	X	X
Karnofsky Score	X												
Height	X												
Weight	X		X	X	X	X	X	X	X	X	X	X	X
Signs/Symptoms/ Diagnoses			X	X	X	X	X	X	X	X	X	X	X
Concomitant/TB/ ARV Medications			X	X	X	X	X	X	X	X	X	X	X
Complete Blood Count with Differential	X		X							X		X	X
Complete Blood Chemistry Profile	X		X							X		X	X
CD4+ Count (HIV-infected participants)	X												
Pregnancy Test	X[1]		X										
NAT2 genotype (blood and saliva)			X										
Chest X-ray	X[2]												
Spot Sputum Collection			X[3]										
Genotypic DST			X										

Evaluation	Screening	Pre-entry	Entry: Registration/ Randomization	Study Treatment (Days)							Discharge	Final Visit	Premature Discontin-uation
			Step 2 Day 0	1	2	3	4	5	6	7	Day 8	Day 21 +/-3	
(MTBDR*sl*)[4]													
Overnight Sputum Collection		X	X	X	X	X	X	X	X	X			
EBA Analysis by Solid Culture CFU Determination and Liquid MGIT Culture for TTD[5]		X	X	X	X	X	X	X	X	X			
Pharmacokinetic Sampling									X				
Hospitalization	X[6]	X	X	X	X	X	X	X	X	X			

[1]Participants must have a negative serum or urine pregnancy test within 7 days prior to entry.
[2]A chest x-ray is not required at screening if results of a chest x-ray performed within 14 days prior to screening are available.
[3]Sputum from Step 1 (Screening or Day 0) may be used if there is an adequate amount for genotypic DST.
[4]For those participants who have MDR-TB identified by MTBDR*plus.*
[5]X's here refer to the date that the overnight sputum collection was begun. Assay will be conducted the next morning.
[6]At the discretion of the investigator, some participants may be hospitalized during the screening evaluations, but this is not a requirement.

4.3 Analyses of Outcomes Measures

4.3.1 Primary outcomes

This is a per-protocol analysis in the efficacy population defined in Section 3.1. The primary endpoint is EBA0-7(CFU), which is defined in Section 3.2. Descriptive statistics of EBA0-7(CFU) with N, mean (s.d.), median (IQR), min, and max for each of the cohorts will be reported. Box plot of EBA0-7(CFU) with Q1, median, mean, and Q3 and plot with 95% confidence intervals for the mean EBA0-7(CFU) will be created for each cohort. Note: The analysis for this outcome will be performed for Group 1 and Group 2.

Another primary endpoint is EBA0-7(TTD), which is defined in Section 3.2. Descriptive statistics of EBA0-7(TTD) with N, mean (s.d.), median (IQR), min, and max will be reported by each cohort. Box plot of EBA0-7(TTD) with Q1, median, mean, and Q3 and plot of 95% confidence interval for the mean EBA0-7(TTD) will be created for each cohort.

New grade 2 or higher signs and symptoms, as well as laboratory events will be summarized in a table using SMR. In addition, all new grade 2 or higher signs/ symptoms and laboratory events with relatedness of treatment and most related drugs.

The PK analysis to examine the relationship between the AUC/MIC and the EBA as described in the protocol Section 9.2.1.2 will be provided in a separate PK analysis plan.

4.3.2 Secondary outcomes

Descriptive statistics of MICs with N, mean (s.d.), median (IQR), min, and max will be summarized by mutation Group (inhA mutation, katG mutation, or neither of these mutations). Box plot of MICs by mutation Group with Q1, median, mean, and Q3, histogram to examine possible bimodal distributions, and plot of 95% confidence interval for the mean MICs by mutation Group will be created.

Nonlinear mixed model using SAS procedure NLMIXED will be fit to estimate the decrease of log10 CFU counts per day for the ‘early’ and ‘terminal’ phase. If there is no clear bi-phase pattern, linear mixed model using SAS procedure MIXED will be used. All available log10 transformed CFU counts at all time points will be included as a dependent variable, and day of the samples will be included as the primary exploratory variable in the model for each cohort. Note: The analysis for this outcome will be performed for Group 1 and Group 2.

Nonlinear mixed model using SAS procedure NLMIXED will be used to estimate the increase of TTD per day for the ‘early’ and ‘terminal’ phase. If there is no clear bi-phase pattern, linear mixed model using SAS procedure MIXED will be used. Log10 transformation may be applied if appropriate. TTD from all time points (excluding results from contaminated samples or re-culture of contaminated samples after addition decontamination) will be included as a dependent variable, and day of the sample will be included as exploratory variable in the model for each cohort.

Additional analyses will be conducted:

- Descriptive statistics of EBA0-2(CFU) with N, mean (s.d.), median (IQR), min, and max for each of the cohorts will be reported. Box plot of EBA0-2(CFU) with Q1, median, mean, and Q3 and plot

with 95% confidence intervals for the mean EBA0-2(CFU) will be created for each cohort. Note: Note: The analysis for this outcome will be performed for Group 1 and Group 2.

- Descriptive statistics of EBA2-7(CFU) with N, mean (s.d.), median (IQR), min, and max for each of the cohorts will be reported. Box plot of EBA2-7(CFU) with Q1, median, mean, and Q3 and plot with 95% confidence intervals for the mean EBA2-7(CFU) will be created for each cohort. Note: The analysis for this outcome will be performed for Group 1 and Group 2.

- Descriptive statistics of EBA0-2(TTD) with N, mean (s.d.), median (IQR), min, and max will be reported by each cohort. Box plot of EBA0-2(TTD) with Q1, median, mean, and Q3 and plot of 95% confidence interval for the mean EBA0-2(TTD) will be created for each cohort.

- Descriptive statistics of EBA2-7(TTD) with N, mean (s.d.), median (IQR), min, and max will be reported by each cohort. Box plot of EBA2-7(TTD) with Q1, median, mean, and Q3 and plot of 95% confidence interval for the mean EBA2-7(TTD) will be created for each cohort.

Note: The analysis of secondary PK endpoints as described in the protocol Section 9.2.2.1 and 9.2.2.3 will be provided in a separate PK analysis plan.

5 Report components

Detailed descriptions of the content of each of the following sections are given in the AIP.

1. Recruitment/Accrual
2. Participants and Data Ineligible for Analysis
3. Baseline Characteristics
4. Completeness of Database
5. Study Status
6. Treatment Status
7. Safety
    - Signs and Symptoms and Laborary Abnormalities
    - Diagnoses
8. Primary Outcomes
9. Secondary Outcomes

Analyses of Group 1 and Group 2 Step 1 and Step 2 and Group 3 Step 1 participants enrolled under Protocol Version 2.0 were complete in 2018. Protocol Version 2.0 did not randomize Group 3 participants to receive any study treatment. Protocol Version 3.0 randomized Group 3 participants who met Step 1 and Step 2 entry criteria to receive 7 days of INH randomized 1:1 to one of two doses: 15 mg/kg or 20 mg/kg. As a result, there will be two separate primary statistical reports for this study:

1. A report Groups 1 and 2 Steps 1 and 2 and Group 3 Step 1 enrolled under Protocol Version 2.0 (complete and dated Septemember 17, 2018)

2. A report covering Group 3 participants enrolled under Protocol version 3.0.

   Note: some basic summaries from participants enrolled under Protocol Version 2.0 may also be included in the second report to provide context.