A5312

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

NIAID CRMS # 11872

This file contains the current ACTG A5312 protocol:

- Letter of Amendment #1, dated 03 August 2020
- Clarification Memorandum #2, dated 25 February 2020
- Clarification Memorandum #1, dated 12 December 2019
- Protocol Version 3.0, dated 21 August 2018

Letter of Amendment #1 for:

A5312

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

NIAID CRMS # 11872

Letter of Amendment Date: 03 August 2020

ACTG NETWORK COORDINATING CENTER
Social & Scientific Systems
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3000
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LETTER OF AMENDMENT

DATE: August 3, 2020

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5312 Protocol Team

SUBJECT: Letter of Amendment #1 for Protocol A5312, Version 3.0

The following information affects the A5312 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by your IRB/EC before implementation.

The following information may also affect the Sample Informed Consent. Your IRB/EC is responsible for determining the process of informing participants of the contents of this LOA.

Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification, along with this letter and any IRB/EC correspondence, should be retained in the site's regulatory file.

This LOA is being implemented to reopen the study to screening and accrual following closure due to COVID-19.

The following is a change to A5312, Version 3.0, 08/21/18, titled "The Early Bactericidal Activity of High-Dose or Standard-Dose Isoniazid among Adult Participants with Isoniazid-Resistant or Drug-Sensitive

Tuberculosis." This change will be included in the next version of the A5312 protocol if it is amended at a future date.

1. A Protocol Signature Page (PSP) is appended for submission to DAIDS Protocol Registration System (DPRS) as part of the LOA registration packet.

2. The study temporarily closed to screening and accrual on March 27, 2020 due to COVID-19. The study is now being reopened to screening and accrual.

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

SIGNATURE PAGE

I will conduct the 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 Conference on Harmonization 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.

Principal Investigator: _____
Print/Type

Signed: _____Date: _____
Name/Title

Clarification Memo #2 for:

A5312

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

NIAID CRMS # 11872

Clarification Memo Date: 25 February 2020

ACTG NETWORK COORDINATING CENTER
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CLARIFICATION MEMO

DATE: February 25, 2020

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5312 Protocol Team

SUBJECT: Clarification Memo #2 for Protocol A5312, Version 3.0

This clarification memo (CM) does not result in a change in the protocol informed consent document. The Division of AIDS does not require you to forward it to your institutional review board (IRB); however, you must follow your IRB's policies and procedures. If IRB review of clarification memos is required at your site, please submit this document for review.

Each site should file a copy of this CM with the protocol for reference.

The protocol clarification contained in this memo should be implemented immediately.

The reason for this CM is to clarify the washout period for drugs with anti-TB activity.

The following is a clarification to Protocol A5312, Version 3.0, 08/21/18, titled "The Early Bactericidal Activity of High-Dose or Standard-Dose Isoniazid among Adult Participants with

Isoniazid-Resistant or Drug-Sensitive Tuberculosis." This clarification will be included in the next version of the A5312 protocol if it is amended at a future date.

- Section 4.4.2 (Exclusion Criterion for Step 2) has been revised to read:

  Receipt of more than 7 cumulative days of second-line anti-TB drugs (including all drugs with anti-TB activity, except INH, RIF, ethambutol, pyrazinamide, and streptomycin) and/or antibiotics intended for bacterial treatment that may have anti-TB activity, including amoxicillin/clavulanate (Augmentin), linezolid, metronidazole, or drugs from the quinolone class, within the 14 days prior to Step 1 screening sputum collection.

  NOTE: In participants who have received 7 days or less of these drugs, the minimum washout period for these drugs is 7 days prior to Step 2 pre-entry sputum collection, regardless of how many cumulative days, up to a maximum of 7 days, the drugs have been taken.

Clarification Memo #1 for:

A5312

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

NIAID CRMS # 11872

Clarification Memo Date: 12 December 2019

ACTG NETWORK COORDINATING CENTER
Social & Scientific Systems
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3000
Fax: 301-628-3302

CLARIFICATION MEMO

DATE: December 12, 2019

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5312 Protocol Team

SUBJECT: Clarification Memo #1 for Protocol A5312, Version 3.0

This clarification memo (CM) does not result in a change in the protocol informed consent document. The Division of AIDS does not require you to forward it to your institutional review board (IRB); however, you must follow your IRB's policies and procedures. If IRB review of clarification memos is required at your site, please submit this document for review.

Each site should file a copy of this CM with the protocol for reference.

The protocol clarifications contained in this memo should be implemented immediately.

The main reason for this CM is to clarify the target accrual for the study. In addition, the ACTG Web site address has been updated, and the laboratory requirement for CD4+ count testing has been updated to comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials.

The following are clarifications to Protocol A5312, Version 3.0, 08/21/18, titled "The Early Bactericidal Activity of High-Dose or Standard-Dose Isoniazid among Adult Participants with Isoniazid-Resistant or Drug-Sensitive Tuberculosis." These clarifications will be included in the next version of the A5312 protocol if it is amended at a future date.

1. There were 259 total participants enrolled in A5312 prior to the implementation of Version 3.0; this includes 64 participants who were enrolled in Group 3, Step 1. Under Version 3.0, the target accrual for Group 3, Step 2, is 20 participants. Since some participants who screen for the study will qualify for Step 1 and not for Step 2, it is expected that 20 additional participants will enroll in Group 3, Step 1 only. Thus, the total accrual for the study is 299 participants (259 under Version 2.0, and 40 participants under Version 3.0). Participants in Group 3, Step 2, who discontinue before the day 7 sample collection will be replaced and are not included in the calculation for target accrual. Below is the breakdown of enrollment by group and step:

Group	Step	Actual Accrual prior to Version 3.0	Expected Accrual under Version 3.0	Target Accrual (Actual + Expected)
1	1 only	66		66
	1 + 2	44		44
2	1 only	69		69
	1 + 2	16		16
3	1 only	64	20	84
	1 + 2		20	20
				Total: 299

2. Study Management, Copies of the Protocol: The text has been revised to read:

   To request hard copies of the protocol, send a message to ACTGNCC@s-3.com via e-mail. Electronic copies can be downloaded from the ACTG Web site **(https://actgnetwork.org)**.

3. Section 4.3, Inclusion Criteria for Step 2, Criterion 4.3.6:

   For HIV-positive candidates only: CD4+ count of ≥50 cells/mm^3, performed within 7 days prior to entry at **any network-**approved laboratory that **is IQA-certified**.

4. Section 6.3, Instructions for Evaluations. The following language has been added as the first paragraph in this section:

   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/sites/default/files/laboratorypolicy1.pdf.

5. Section 6.3.7, Laboratory Evaluations, CD4+ Count (HIV-infected participants):

   For participants who are HIV-infected, a CD4+ count determination performed within 7 days prior to entry at **a network-approved laboratory that possesses IQA certification** must be recorded.

A5312

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

A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by:

The National Institute of Allergy and Infectious Diseases

Non-IND

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FINAL Version 3.0
August 21, 2018

ACTG
AIDS CLINICAL TRIALS GROUP

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

SIGNATURE PAGE

I will conduct the 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 U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization 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.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

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SITES PARTICIPATING IN THE STUDY

Task Applied Science and Brooklyn Chest Hospital, Cape Town, South Africa, will serve as clinical sites for Stage 1 and Stage 2.

Additional sites may be added for Stage 1 or Stage 2. Please see the A5312 protocol-specific web page (PSWP) for a list of participating sites.

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STUDY MANAGEMENT

All **general** questions concerning this protocol should be sent to actg.teamA5312@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.teamA5312@fstrf.org. A response should generally be received within 24 hours (Monday-Friday).

Protocol E-mail Group
Sites registering to this study should contact the Computer Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5312 e-mail group. Include the protocol number in the e-mail subject line.

- Send an e-mail message to actg.user.support@fstrf.org.

Clinical Management
For questions concerning entry criteria, toxicity management, concomitant medications, and coenrollment, contact the protocol co-chairs. Send an e-mail message to actg.cmcA5312@fstrf.org (ATTN: Kelly Dooley, MD, PhD, or Andreas Diacon, MD). Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
For questions specifically related to pharmacologic laboratory tests, contact the protocol pharmacologist. Send an e-mail message to actg.teamA5312@fstrf.org (ATTN: Helen M. McIlleron, MB ChB, PhD).

Data Management
For nonclinical questions about transfers, inclusion/exclusion criteria, case report forms (CRFs), the CRF schedule of events, randomization/registration, delinquencies, and other data management issues, contact the data manager.

- For transfers, reference the Patient Transfer from Site to Site SOP 119, and contact Kathleen Donahue, BS, MA (donahue@fstrf.org) directly.
- For other questions, send an e-mail message to actg.teamA5312@fstrf.org (ATTN: Kathleen Donahue, BS, MA). Include the protocol number, PID, and a detailed question.

Randomization
For randomization questions or problems and study identification number (SID) lists.

- Send an e-mail message to rando.support@fstrf.org or
- Call the Statistical and Data Analysis Center (SDAC)/DMC Randomization Desk at (716) 834-0900 x7301.

Computer and Screen Problems
Contact the SDAC/DMC programmers.

- Send an e-mail message to actg.support@fstrf.org or call (716) 834-0900 x7302.

Protocol Document Questions
For questions concerning the protocol document, contact the clinical trials specialist. Send an e-mail message to actg.teamA5312@fstrf.org (ATTN: Laura Moran, MPH).

Copies of the Protocol
To request hard copies of the protocol, send a message to ACTGNCC@s-3.com (ATTN: Diane Delgado) via e-mail. Electronic copies can be downloaded from the ACTG Web site (https://www.actgnetwork.org).

Product Package Inserts or Investigator Brochures
To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call (301) 897-1708.

Protocol Registration
For protocol registration questions:

- Send an e-mail message to Protocol@tech-res.com or call (301) 897-1707.

Study Product
For questions or problems regarding study product, dose, or supplies, call Lynette Purdue, protocol pharmacist, at 240-627-3061.

Expedited Adverse Event (EAE) Reporting/Questions
Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or fax 1-800-275-7619 or 301-897-1710.

Phone Calls
Sites are responsible for documenting any phone calls made to A5312 protocol team members. Send an e-mail to actg.teamA5312@fstrf.org.

Protocol-Specific Web Page
Additional information about the study may be found on the A5312 protocol-specific web page (PSWP).

PROTOCOL-SPECIFIC GLOSSARY OF TERMS

CFU	Colony-forming unit
DR-TB	Drug-resistant tuberculosis
DS-TB	Drug-sensitive tuberculosis
DST	Drug susceptibility testing
EBA	Early bactericidal activity
EBA_{0-7} (CFU)	Early bactericidal activity over 7 days measured by the daily fall of log_{10}CFU/mL sputum
EBA_{0-7} (TTD)	Early bactericidal activity measured by prolongation of TTD/day
MDR-TB	Multidrug-resistant tuberculosis
MGIT	Mycobacterium growth indicator tube
MIC	Minimum inhibitory concentration
NAT2	N-acetyltransferase 2
TTD	Time to detection
XDR-TB	Extensively drug-resistant tuberculosis

SCHEMA

A5312

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

DESIGN

A two-stage, two-step, phase IIa, open-label, randomized clinical trial examining the bactericidal activity of (1) isoniazid (INH) at three different doses for treatment of isolates with *inhA* mutations**; (2) INH at two different doses for treatment of isolates with *katG* mutations; and (3)** INH at standard dosing for isolates without either *inhA* or *katG* mutations. In addition, the association between the early bactericidal activity (EBA) and pharmacokinetic (PK) parameters, such as area under the curve (AUC)/minimum inhibitory concentration (MIC) of INH, will be examined among participants with drug-resistant TB (DR-TB), and drug-sensitive TB (DS-TB) (when Stage 2 opens).

The study will be conducted in two stages. Stage 1 will be a pilot for determination of feasibility and sample size verification, and Stage 2 will be the main study. These stages will be conducted sequentially, and a participant may enroll in only one of the stages.

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 DR-TB (both stages) 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.

Eligible participants will enroll into one of three groups:

Group 1: Participants with AFB smear-positive pulmonary TB with an *M. tuberculosis* isolate with an inhA mutation only, which generally confers low-level INH resistance. During Stage 1 and Stage 2, participants who meet

Step 1 and Step 2 entry criteria will be randomized to receive INH at 5, 10, or 15 mg/kg daily for 7 days. Participants who do not meet Step 2 criteria will be enrolled in Step 1 only.

Group 2: Participants with *M. tuberculosis* harboring neither *inhA* nor *katG* resistance mutations. During Stage 1, eligible participants will be enrolled in Step 1 only. During Stage 2, participants who meet Step 1 and Step 2 entry criteria will be enrolled as positive controls. Also during Stage 2, participants not eligible to enter Step 2 and participants recruited after Step 2 accrual targets have been met may be enrolled in Step 1.

Group 3: Participants with an *M. tuberculosis* isolate with a *katG* mutation (with or without an *inhA* mutation), associated with high-level resistance. **During Stage 2, participants who meet Step 1 and Step 2 entry criteria will be randomized 1:1 to receive either INH 15 mg/kg or 20 mg/kg daily for 7 days. Participants who do not meet Step 2 criteria will be enrolled in Step 1 only.**

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).

DURATION Approximately 23 days

SAMPLE SIZE Among participants eligible to participate in Step 1 only, accrual targets are as follows:

Group 1: Minimum of 16 to a maximum of 70
Group 2: Minimum of 48 to a maximum of 64
Group 3: **Minimum of 64 to a maximum of 84**

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). During Stage 1, 15 Group 1 participants will be enrolled (5 per dosing cohort). Once it is determined that the study is feasible, Stage 2 will begin 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: 20 evaluable participants (10 completing treatment in each dosing cohort) will be randomized.

At the end of Stage 1, the sample size for enrollment in the treatment cohorts may be increased up to 88 evaluable participants (22 in each treatment cohort) if the standard deviations of the primary endpoint from Group 1 are larger than expected.

Schema Table 1: A5312 Accrual Targets

	Resistance Mutation	Participants Completing Step 1 Only[1]	Participants Completing Step 1 and Step 2[2]		Total Participants
		Stage 1 & Stage 2 Combined	Stage 1	Stage 2	
Group 1	*inhA*	Minimum of 16 to a maximum of 70[3]	15 (5 per dosing cohort)	33 (11 per dosing cohort)	Step 1 only: maximum of 70[3] Steps 1 and 2: 48
Group 2	Neither *inhA* nor *katG*	Minimum of 48 to a maximum of 64[4]	-	16	Step 1 only: maximum of 64[4] Steps 1 and 2: 16
Group 3	*katG* with or without *inhA*	**Minimum of 64 to a maximum of 84**	-	**20 (10 per dosing cohort)**	**Step 1 only: maximum of 84[5]** **Steps 1 and 2: 20**

[1] Participants completing Step 1 only (participants who were considered for Step 2 but could not enter Step 2, or participants who were considered for Step 1 only) will provide sputum for determination of MIC distribution, and then be discontinued from the study.

[2] Participants completing Step 1 and Step 2 will provide sputum for determination of MIC distribution and participate in the treatment part of the study.

[3] Once the Group 1 accrual target is reached for participants completing Steps 1 and 2, accrual beyond the minimum for those completing Step 1 only will stop.

[4] Once the Group 2 accrual target is reached for participants completing Steps 1 and 2, accrual beyond the minimum for those completing Step 1 only will stop.

[5] Once the Group 3 accrual target is reached for participants completing Steps 1 and 2, accrual beyond the minimum for those completing Step 1 only will stop.

POPULATION Patients between 18 and 65 years old with sputum smear-positive pulmonary TB (new or retreatment cases)

REGIMEN

Participants enrolled in Step 1 only will not receive study drug.

Participants enrolled in Step 2 will receive study drug as follows:

Group 1: Participants with M. tuberculosis with an inhA mutation only who meet Step 2 entry criteria will be randomized 1:1:1 to receive the following treatments for 7 days:

5 mg cohort: INH 5 mg/kg daily plus vitamin B6 ≥25 mg daily
10 mg cohort: INH 10 mg/kg daily plus vitamin B6 ≥25 mg daily
15 mg cohort: INH 15 mg/kg daily plus vitamin B6 ≥25 mg daily

Group 2: Participants with M. tuberculosis with neither katG nor inhA mutations who meet Step 2 entry criteria will receive INH 5 mg/kg daily plus vitamin B6 ≥25 mg daily for 7 days.

Group 3: Participants with an *M. tuberculosis* isolate with a *katG* mutation with or without an *inhA* mutation **who meet Step 2 entry criteria will be randomized to receive either INH 15 mg/kg or 20 mg/kg daily, plus vitamin B6 ≥25 mg daily for 7 days.**

1.0 HYPOTHESES AND STUDY OBJECTIVES

1.1 Hypotheses

1.1.1 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 log_{10} colony-forming unit (CFU)/mL sputum over 7 days (EBA_{0-7} (CFU)) that is at least 50% the EBA_{0-7} (CFU) of standard-dose isoniazid (INH) when given to participants with drug-sensitive TB (DS-TB).

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

1.1.3 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.**

1.2 Primary Objectives

1.2.1 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).

1.2.2 Estimate the 7-day EBA, based on 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).

1.2.3 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.

1.2.4 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.

1.3 Secondary Objectives

1.3.1 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).

1.3.2 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.

1.3.3 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 EBA_{0-7} of standard-dose INH when given to participants with DS-TB, by dose.

1.3.4 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,** and participants infected with DS-TB taking standard-dose INH (5 mg/kg daily).

1.4 Exploratory Objectives

1.4.1 Evaluate the correlation between EBA_{0-7} (TTD) and EBA_{0-7} (CFU) among participants with smear-positive pulmonary TB.

1.4.2 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.

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

2.0 INTRODUCTION

2.1 Background

Drug-resistant tuberculosis (DR-TB), including multidrug-resistant (MDR-) and extensively drug-resistant (XDR-) TB, is increasingly a global health threat [1]. MDR-TB is resistant to isoniazid (INH) and rifampin (RIF), while XDR-TB is resistant to INH, RIF, fluoroquinolones, and injectable anti-TB drugs. Therapeutic options are few, and current treatment requires 18-24 months of highly toxic, poorly efficacious multidrug therapy. There are new drugs in the pipeline, but these compounds must be combined with an optimized background regimen that includes partner drugs that can rapidly reduce mycobacterial burden, thus protecting the new drug against the development of clinical resistance [2, 3]. Having a potent combination of 3-4 drugs with good activity against *M. tuberculosis* in a regimen is essential to prevent acceleration of resistance and progression from MDR-TB to XDR-TB. The World Health Organization (WHO) recommends that regimens for MDR-TB or XDR-TB contain at least four drugs to which the organism is likely to be sensitive [4]. A common standard regimen, for example, may include kanamycin (ototoxicity, poor bactericidal activity), ofloxacin (not the most active fluoroquinolone but gatifloxacin [hypoglycemia] and moxifloxacin [QT prolongation] carry safety risks), ethionamide (dose-limiting GI toxicity), PZA (risk of resistance, as this drug is a standard part of first-line regimens), cycloserine (severe CNS toxicity), and ethambutol (ophthalmologic toxicity risk and risk of resistance, as this drug is a standard part of first-line regimens). Phenotypic drug susceptibility testing (DST) can guide

therapy, but results can take 1-2 months and are only available if a culture can be grown. Clearly, we must do a better job of identifying drugs to which a participant's TB isolate is likely to be susceptible at the time of MDR-TB diagnosis.

For INH, different resistance mechanisms confer high- or low-level resistance. Low-level "resistance" may be overcome by increasing the INH dosage. Pharmacodynamic (PD) studies in a variety of experimental models and in humans, coupled with data on the range of INH MIC values against INH-resistant clinical isolates, suggest that high-dose INH may produce drug exposures capable of significant bactericidal activity in participants with TB with low-level INH resistance [5-12].

INH is cheap, widely used, orally bioavailable, safe, and generally free of drug-drug interactions. It has potent EBA and plays an important role in rapidly reducing the bacterial burden and preventing the selection of drug-resistant mutants [7, 13]. Against drug-susceptible strains, INH alone is able to decrease the bacterial burden by 90-95% in the first two days of treatment. Although INH exposures are influenced by the patient's acetylator status, near maximal activity against drug-susceptible strains is observed at the commonly prescribed dose, even in rapid acetylators. INH is a prodrug that is activated by the *M. tuberculosis* catalase-peroxidase encoded by *katG* [6]. The activated drug inhibits the activity of the enoyl-acyl carrier protein reductase (*inhA*) and thereby blocks mycolic acid synthesis [14]. Against susceptible strains of *M. tuberculosis,* the MIC is 0.03-0.06 mcg/mL. Mutations in the *katG* gene may result in partial loss of KatG function, resulting in reduced INH activation and INH MICs of 2 to 8 mcg/mL or, alternatively, complete loss of KatG function, no INH activation, and INH MICs ≥16 mcg/mL. On the other hand, mutations in *inhA* and the *inhA* promoter region are associated with low-level resistance (MIC 0.2-1 mcg/mL) and cross-resistance with ethionamide. Data on the distribution of INH MICs against clinical DR-TB isolates are sparse [15], but reports suggest *inhA* mutations account for 30-40% of INH-R strains, and as many as 43-75% of MDR-TB strains are susceptible to INH concentrations <5 mcg/mL [16]. Since INH concentrations well above this level are achievable in patients receiving INH in moderately elevated dosages (higher-dose INH), patients infected with low-level-resistant strains may represent a substantial sub-population of DR-TB in which high-dose INH may be effective.

In experimental TB models, AUC/MIC is the PD parameter most closely correlated with INH activity [10, 11]. AUC/MIC values of ~60 and 100-200 mcg-h/mL produced 50% and 100%, respectively, of the maximal INH effect in vitro as well as in mice. A similar relationship is evident in human EBA studies (*vide infra*) [13]. Assuming INH AUC/MIC values approaching 60 mcg-h/mL could be achieved, significant bactericidal activity against "resistant" strains would be expected. This concept is supported by experiments in mice, in which INH at 10 mg/kg/day produced an AUC/MIC of approximately 40 mcg-h/mL and exhibited bactericidal activity against an *inhA* promoter mutant (MIC 0.25 mcg/mL), but was ineffective against a *katG* mutant (MIC 4-8 mcg/mL) against which the AUC/MIC was ≤2 (Nuermberger, unpublished data). Similarly, bactericidal activity was observed with INH 25 mg/kg/day in mice infected with a *katG* mutant with an INH MIC of 2 mcg/mL, where the predicted AUC/MIC would be ~15 [12].

In humans, INH exposures are variable and determined largely by the patient's NAT2 genotype [9, 17]. Fast acetylators have lower INH concentrations than slow or intermediate acetylators taking the same dose, and the distribution of fast acetylators varies by geographical region (33% in the United States and 88% in China, for example) [10]. Attainment of an AUC greater than 10.5 mcg-h/mL, which generally occurs in slow acetylators at a 3 mg/kg dosage and for most rapid acetylators at a 6 mg/kg dosage, was associated with 90% of maximal EBA, and this is consistent with the AUC/MIC >100 mcg-h/mL necessary for maximal INH activity in pre-clinical models [13]. Assuming the INH AUC/MIC necessary to achieve 50% of the maximum kill is similar among patients with DS-TB and DR-TB, significant bactericidal activity against low-level resistant strains (MIC ≤0.5 mcg/mL) can be expected with AUC values of approximately 25 (AUC/MIC ≥50). Such exposures should be achievable with 300 mg of INH (5 mg/kg, standard-dose INH) in slow acetylators and 600 mg of INH (10 mg/kg, high-dose INH) in fast acetylators. Higher INH doses may produce activity against strains for which the INH MIC is 1, or even 2, mcg/mL, depending on acetylator status. For example, in one PK study in healthy Japanese participants who were fast acetylators, a 900 mg (15 mg/kg) dose produced a mean AUC of 48.2 mcg-h/mL, which would produce AUC/MIC values of ~50 and ~25 against isolates for which INH MICs are 1 and 2 mcg/mL, respectively [18].

In addition to such arguments based on PDs, indirect clinical evidence that high-dose INH inhibits or kills low-level INH-resistant organisms comes from a randomized trial in which low-level INH resistance (MIC <5 mcg/mL) was less likely to emerge in slow acetylators receiving 8-9 mg/kg of INH as monotherapy, compared to slow acetylators receiving 4-5 mg/kg or rapid acetylators receiving either dose, whereas high-level INH resistance was more common among slow acetylators receiving the higher dose [19]. **Three** recent observational trials that demonstrated high success rates of "short-course" MDR-TB treatment (9-12 months) used multidrug treatment regimens that included high-dose INH. In the first study in Bangladesh [20], the most effective regimen involved an intensive phase of at least 4 months during which participants received high-dose INH (10-12 mg/kg). **Notably, the investigators from the Bangladesh study indicated that the majority of patients in the study had TB with INH resistance mediated by *katG* mutations. They observed that the most frequent *katG* mutation (315) confers a range of MIC values but that the majority of strains have resistance levels around the peak serum concentration of standard-dose INH (5 mg/kg); they further stated that high-dose isoniazid would, thus, be active against the majority of strains with *katG* mutations [21]. To wit, in prospective observational studies in Cameroon and Niger that followed the work in Bangladesh [22, 23], the efficacy of a 'Bangladesh-type regimen' that included standard- or high-dose INH among patients with MDR-TB was** similarly impressive**, even among those patients with medium- to high-level INH resistance.** In a randomized controlled trial in India, participants with MDR-TB **(no information about mechanism of INH resistance)** were randomized to high-dose INH (16-18 mg/kg), standard dose INH (5 mg/kg), or placebo, each together with a standardized background regimen [**24**]. Six-month culture conversion rates were 74%, 45%, and 49%, respectively, with times to culture conversion shortened with high-dose

INH (3.4 vs. 6.4 vs. 6.6 months). The relationship between INH MIC and/or acetylator status and treatment outcomes was not explored in this study. Of note, peripheral neuropathy was more common among those receiving high-dose INH. However, vitamin B6 supplementation was not given [**25**]. Hepatotoxicity rates were not different among groups, with relative risk of hepatotoxicity comparing high-dose INH to standard-dose INH and placebo groups of 0.96 (95% CI 0.54-1.74). Other trials have shown no benefit of adding standard dose INH, but improved outcomes when adding high-dose INH to retreatment regimens [**26, 27**]. **Of note, doses of INH up to 20 mg/kg have been studied and are well-tolerated, but there is limited safety information for doses higher than that [24, 28-30].**

INH Drug Information

INH is the hydrazide of isonicotinic acid and is one of the primary drugs for TB treatment. The activity of INH is limited to the mycobacteria of the *M. tuberculosis* complex. The probable mechanism of action is the inhibition of the biosynthesis of mycolic acids, a component of the mycobacterial cell wall.

Dose and indications

INH is U.S. Food and Drug Administration (FDA)-approved for the treatment of active TB in combination with other appropriate anti-TB medications, and as a single agent for TB preventive therapy (treatment of latent TB infection). The approved dose is 5 mg/kg up to 300 mg daily or 15 mg/kg up to 900 mg twice or thrice weekly**, given for 6-9 months**. **In the Companion Handbook of the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis, the dose recommended for high-dose INH for patients with drug-resistant TB is for 16-20 mg/kg once daily. The WHO recently produced guidelines for treatment of INH-resistant TB in which they suggested a dose of up to 15 mg/kg daily [31].** In this study, participants will receive 5, 10, 15**, or 20** mg/kg daily for 7 days to evaluate the activity of INH against *M. tuberculosis* organisms that harbor resistance mutations to INH.

Pharmacokinetics

INH is generally well absorbed; food and antacids decrease the rate, but not the extent of absorption. The peak blood levels of INH, 3 to 5 mcg/mL, are obtained 30 minutes to 2 hours after ingestion of routine doses [**32**]. It diffuses into all body fluids and cells and penetrates into the caseous material of a tuberculoma or pulmonary cavity. In the liver, it is acetylated to inactive metabolites, and 75% to 95% of the dose is excreted as inactive metabolites in the urine within 24 hours. INH clearance rates depend on NAT2 metabolizer genotype, which is associated with race but not gender [**33**]. The INH AUC among “fast acetylators” is 30% to 50% of that among “slow acetylators.” Because INH is well tolerated over a wide range of therapeutic doses, a single dose is recommended, regardless of weight or acetylator status. Persons who have rapid acetylation achieve effective concentrations, while persons who have slow acetylation do not experience increased toxicity. Half-life ($T_{1/2}$) may vary from 1 hour in fast acetylators ($T_{1/2}$ < 90 min) to 3 hours in slow acetylators ($T_{1/2}$ >90 min).

Drug-drug interactions
INH decreases the clearance of some medications that are metabolized in the liver (particularly carbamazepine, phenytoin, and diazepam) [**34**]. However, in the context of multidrug therapy including RIF, these potential drug-drug interactions are of little significance because the effect of INH is counteracted by the more potent opposing effect of RIF [**35**].

Toxicity
The total incidence of all adverse effects from INH at standard doses **given for full treatment duration** is approximately 5%, many of which do not require discontinuation of the drug. Peripheral neurotoxicity is dose **and duration** dependent, and it is uncommon (<0.2%) at conventional doses. The risk of peripheral neuritis increases for persons who are malnourished or predisposed to neuritis by other illnesses. Concomitant administration of pyridoxine (vitamin B6) is recommended for these persons, and will be given to all participants receiving concomitant INH in this trial. Other nervous system reactions are rare at normal doses, and they include convulsions, encephalopathy, optic neuritis, memory impairment, and psychosis. Gastrointestinal adverse effects include nausea, vomiting, and epigastric distress. Asymptomatic elevation of aminotransferases is common and occurs in 10-20% of persons receiving INH. However, idiosyncratic severe hepatic reactions are uncommon, but are more likely in older persons (up to 2.3% hepatitis incidence in persons over 50 years old) and may be life threatening. Daily consumption of alcohol increases the risk of INH-associated hepatotoxicity by approximately four-fold. The risk of INH-induced hepatotoxicity may also be increased in the postpartum period. The prodromal symptoms of hepatotoxicity are anorexia, nausea, vomiting, fatigue, malaise, and weakness; persons who take INH and have these symptoms should stop therapy and be evaluated immediately. **Doses of 16-18 mg/kg given for a full treatment course together with second-line drugs for MDR-TB in a randomized clinical trial were safer and did not have higher risk of hepatotoxicity than standard-dose (5 mg/kg) INH [24]. In patients enrolled in the inhA arms in this trial (A5312), there have been no Grade 3 or higher treatment-related adverse events (AEs). No peripheral neuropathy has been detected.**

2.2 Rationale

In summary, high-dose INH may be useful in the treatment of TB infection commonly considered INH resistant, but its efficacy will likely depend on the dosage and the degree of resistance. In participants infected with TB with isolated *inhA* mutations, **moderate to** high-dose INH **is likely to be** effective. Participants infected with TB with *katG* mutations **may** derive a therapeutic benefit**, provided the dose of INH is sufficiently high. Genotypic** tests that can detect the most common *inhA* and *katG* mutations conferring INH resistance with a short turnaround time directly from sputum have been developed (Hain MTBDR*plus*), and their use is endorsed by the World Health Organization (WHO) [**36, 37**]. These tests can quickly identify participants who are likely to benefit from high-dose INH. Hain MTBDR*plus* also detects mutations associated with RIF resistance. Another rapid test, Gene Xpert, detects RIF resistance and has become an important tool for diagnosis of MDR-TB. In South Africa and in other settings, sputum of patients is tested first with Gene Xpert; if RIF resistance is detected, then the Hain test is used to

see if there is also INH resistance and confirm MDR-TB. Once MDR-TB is identified, patient sputum is sent for phenotypic drug sensitivity tests for first-line and second-line TB drugs. For those patients who are very ill and require immediate treatment, an empiric MDR regimen is given; for others, therapy is held until Hain results are available, treatment history can be reviewed, and the appropriate treatment can be chosen and made available to the clinic serving the patient (a process that takes at least 1-2 weeks). **Gene Xpert testing that will test for both RIF and INH resistance at the time of diagnosis (and includes testing for *inhA* and *katG* mutations) is currently under development. Thus, information about the type of INH resistance will soon be available at the start of MDR-TB treatment.** We believe that patients with MDR-TB with *inhA* mutations can benefit from **moderate- to** high-dose INH. **It is also likely that many patients with MDR-TB with *katG* mutations can benefit from high-dose INH**. Whether and at which dosage high-dose INH can **overcome INH** resistance conferred by *inhA* or *katG* mutations can be assessed using an EBA study, in which daily quantitative sputum cultures are collected from patients with sputum smear-positive pulmonary TB **[38-41].**

In this phase IIa EBA study including participants with INH monoresistant-TB and MDR-TB, we propose combining genotypic and phenotypic INH susceptibility testing, population PK, and PDs to determine the relationship between INH AUC/MIC and bactericidal activity. The study will determine whether or not higher-dose INH has a role in the treatment of TB infection with a bacterium resistant to INH, and if it can be used, the study will enable an optimized dosing strategy based on rapid genotypic tests available at the initiation of TB therapy, a novel approach.

3.0 STUDY DESIGN

This is a two-stage, two-step, phase IIa, open-label, randomized clinical trial among adult participants with sputum smear positive pulmonary TB evaluating the EBA of three different doses of INH among participants infected with *M. tuberculosis* with *inhA* mutations (Group 1). In addition, the EBA of INH among participants with *M. tuberculosis* with no genotypic evidence of INH resistance (Group 2) will be determined. Among participants infected with an *M. tuberculosis* strain with *katG* mutations (Group 3), **the EBA of INH at a dose of 15 or 20 mg/kg will be determined. These doses are selected because doses of up to 15-20 mg/kg appear to be safe (in other studies, as well as in the 15 mg/kg dosing cohort in Group 1 in the current trial) and the safety of doses higher than 20 mg/kg has not been established. In addition, upon preliminary assessment of the EBA data in the *inhA* arms, INH demonstrated activity, and this activity appeared to be dose-related.**

No study drug is administered under Step 1. Data collected in Step 1: (a) determine eligibility to Step 2, and (b) allow characterization of INH MICs in three groups (secondary objective). Groups 1, 2, and 3 consist of participants infected with TB with *inhA* mutations, with DS-TB and with TB with *katG* resistance-conferring mutations, respectively.

The study's primary objectives are addressed via Step 2 evaluations. Participants enrolling to Step 2 receive the study drug, INH, which will be given with vitamin B6 ≥25 mg daily, by mouth. During both stages, participants in Group 1 who meet Step 2 entry criteria will be randomized to receive 5, 10, or 15 mg/kg of INH daily for 7 days. During Stage 2, participants in Group 2 who meet Step 2 entry criteria will receive 5 mg/kg of INH daily for 7 days. **During Stage 2, participants in Group 3 who meet Step 2 entry criteria will be randomized 1:1 to receive 15 or 20 mg/kg of INH daily for 7 days.** After completion of 7 days of INH alone, participants will be referred to begin standard anti-TB chemotherapy according to South African TB Control Programme Guidelines.

In Stage 1, Group 1 participants who do not meet Step 2 entry criteria, all Group 2 participants and all Group 3 participants will be referred to the South African TB Control Programme for treatment. In Stage 2, Group 1 participants who do not meet Step 2 entry criteria, Group 2 participants who do not meet Step 2 entry criteria, and **Group 3 participants who do not meet Step 2 entry criteria** will be referred to the South African TB Control Programme for treatment.

In Step 2, prior to initiation of treatment, sputum will be collected for quantitative culture on solid medium (for CFU **for Groups 1 and 2 only**) and liquid medium (for determination of TTD **for all groups**) and for MIC determination and phenotypic DST. In addition to GenoType MTBDR*plus*, GenoType MTBDR*sl*, which identifies additional mutations associated with resistance to fluoroquinolones **and injectable TB medicines**, will be performed on sputum of participants with MDR-TB (but not INH-monoresistant TB) who are enrolled in the study. Sixteen-hour sputum collections will be performed daily during INH treatment, as per standard EBA methodology [**42**]. Sampling for PK analysis will be performed at steady state on Day 6 (±1). NAT2 genotyping will be performed on a blood sample to help explain variability in INH PK parameters, and a saliva sample will be collected for evaluation of a new rapid NAT2 genotyping test. Safety and tolerability will be monitored via clinical evaluations throughout the study and through scheduled laboratory evaluations.

To avoid unnecessary delay in initiating TB treatment, screening evaluations for Step 1 and Step 2 may occur on the same day.

To minimize risk to study staff and study participants, participants with MDR-TB will be hospitalized on a different ward from participants with DS-TB or INH-monoresistant TB. Strict infection control practices will be followed, including the wearing of N95 masks where appropriate and hospitalization on wards with negative pressure ventilation. In addition, persons with a previous known exposure to XDR-TB or those who have been treated previously for MDR-TB, and thus have a higher risk of XDR-TB, will not be included in this study.

The study will proceed in two stages, as follows:

Stage 1—Pilot study to ensure feasibility:
Participants will be recruited at a single clinical site, Task Applied Science at Brooklyn Chest Hospital, affiliated with Stellenbosch University, in Cape Town, South Africa. All eligible participants will enter Step 1 of the study (determination of INH resistance, measurement of INH MIC). Among Group 1 participants who meet the Step 2 entry criteria, 15 participants will be randomized 1:1:1 to receive 5, 10, or 15 mg/kg daily of INH for 7 days with evaluations performed as described above.

As of March 26, 2015, Stage 1 is complete. A total of 15 Group 1, 44 Group 2, and 12 Group 3 participants were enrolled in Step 1 only during Stage 1. These participants did not receive study treatment. They provided sputum samples for MIC determination.

The goal of Stage 1 will be to demonstrate feasibility, not treatment efficacy. The rate at which the study accrues Group 1 participants at a single site will be assessed after 6 months to determine the advisability of proceeding with Stage 2 and advisability of including additional sites. In addition, the standard deviations (SDs) of the primary endpoint will be reviewed for a possible sample size increase if the SDs in Group 1 are larger than expected.

Stage 2:
During Stage 2, to be conducted at Task Applied Science and other approved sites, Group 1 participants who meet Step 2 entry criteria will be randomized 1:1:1 to receive 5, 10, or 15 mg/kg of INH daily for 7 days until the accrual target (taking together participants who enrolled during Stage 1 and Stage 2) is met. Study drug administration and study procedures will be as described above. In addition, 16 Group 2 participants who meet Step 2 entry criteria will be enrolled and will receive INH at a dose of 5 mg/kg daily, and undergo study procedures as described above. **Also, 20 Group 3 participants who meet Step 2 entry criteria will be enrolled and randomized 1:1 to receive INH at a dose of 15 or 20 mg/kg daily, and undergo study procedures as described above.**

A minimum of 16 to a maximum of 70 Group 1 participants, a minimum of 48 to a maximum of 64 Group 2 participants, and **a minimum of 64 to a maximum of 84** Group 3 participants will be enrolled in Step 1 only during Stages 1 and 2 combined. Participants enrolling to Step 1 only will not receive study drug. They will provide sputum samples for MIC determination.

Figure 3.0-1: Study Design Schematic:

Stage 1:

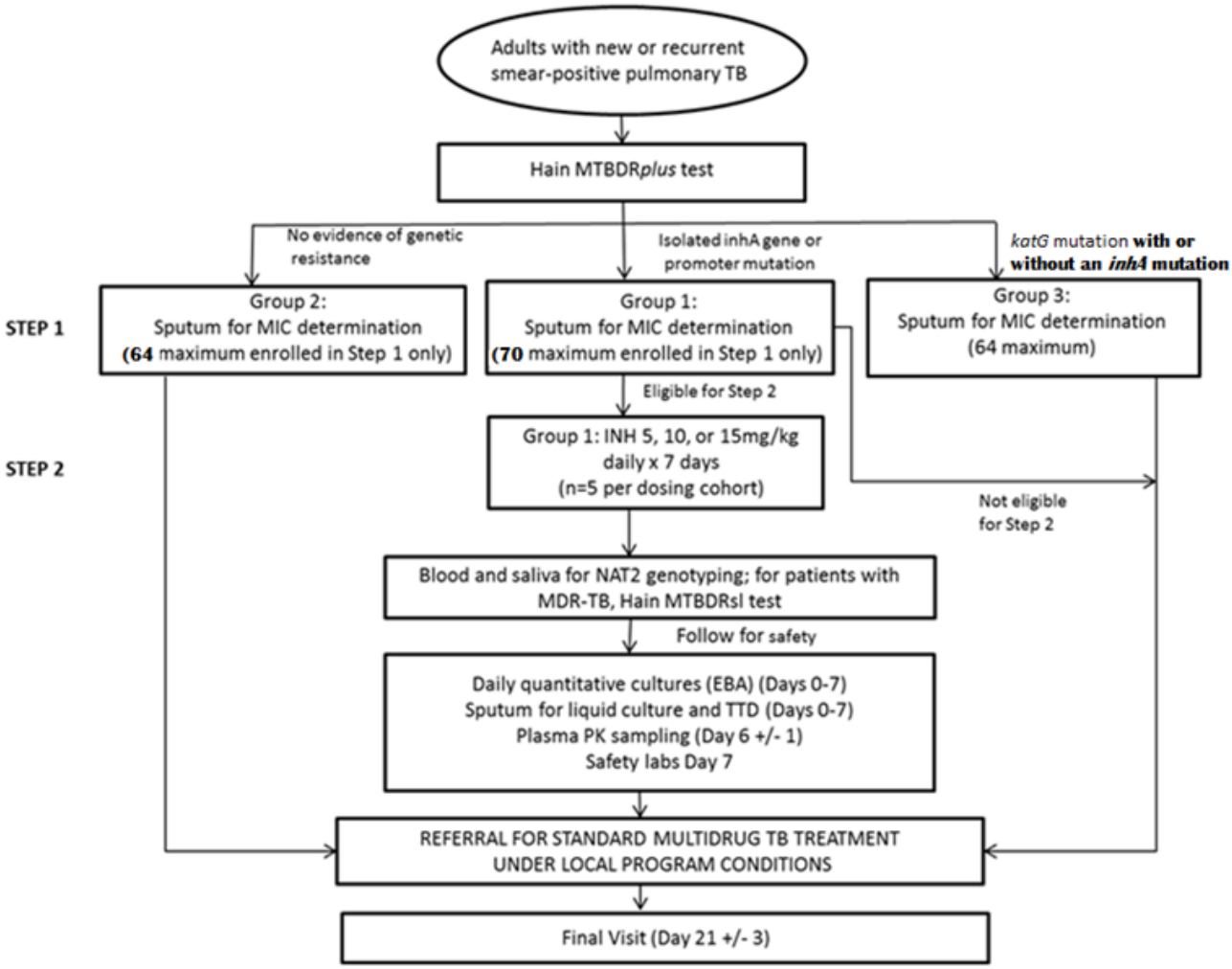
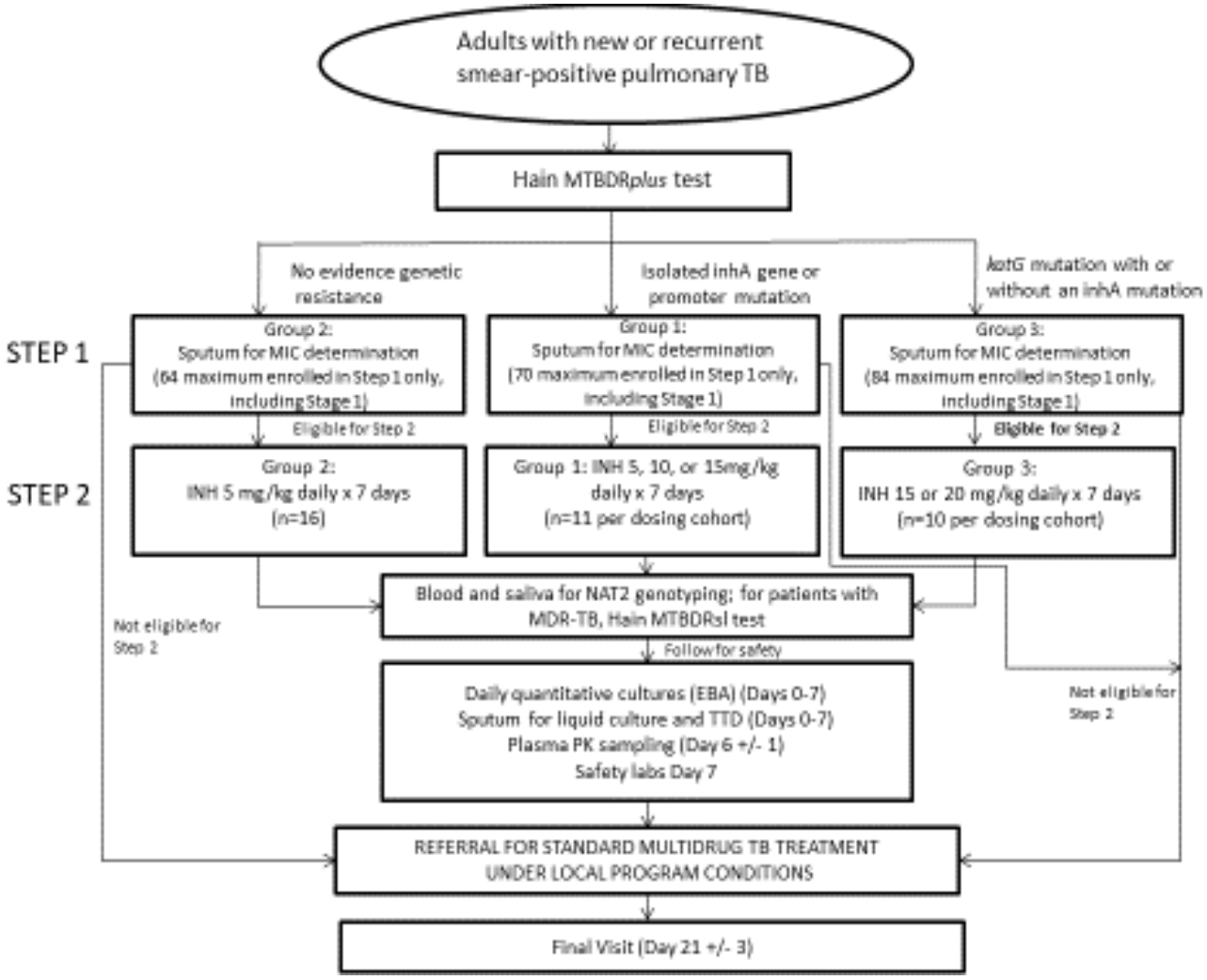


Figure 3.0-2: Stage 2:



4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria for Step 1

4.1.1 New or recurrent pulmonary TB with sputum positive for acid-fast bacilli on direct microscopy of at least grade 1+ (International Union Against Tuberculosis and Lung Disease [IUATLD] scale) at the study laboratory on at least one pre-treatment sputum sample within 14 days prior to entry.

4.1.2 Age ≥18 and ≤65 years at study entry.

4.1.3 Infected with an *M. tuberculosis* strain for which Hain GenoType MTBDR*plus* genotype, performed at the study laboratory within 14 days prior to study entry, reveals one of the following results for INH susceptibility testing:

- *inhA* promoter or functional mutation only (Group 1 participants, eligible for Steps 1 and 2)
- No mutations in the *inhA* or *katG* genes (Group 2 participants, eligible for Step 1 and, during Stage 2 of the study, also eligible for Step 2)
- *katG* mutation with or without an *inhA* mutation (Group 3 participants, **eligible for Step 1 and, during Stage 2 of the study, also eligible for Step 2)**

4.1.4 Ability and willingness of the participant or legal guardian/representative to provide informed consent.

4.2 Exclusion Criteria for Step 1

There are no exclusion criteria for Step 1.

4.3 Inclusion Criteria for Step 2

4.3.1 Entry into Step 1.

4.3.2 <u>During Stage 1 of the protocol</u>: *inhA* promoter or functional mutation only (Group 1).

<u>During Stage 2 of the protocol</u>: *inhA* promoter or functional mutation only (Group 1) OR mutations in neither *inhA* nor *katG* genes (Group 2) **or mutation in the *katG* gene, with or without mutations in *inhA* promoter or functional genes (Group 3).**

4.3.3 Body weight: 40 kg to 90 kg, inclusive.

4.3.4 Laboratory values obtained within 30 days prior to entry:

- Absolute neutrophil count (ANC) ≥750 cells/mm^3
- Hemoglobin ≥7.4 g/dL
- Platelet count ≥50,000/mm^3
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 X upper limit of normal (ULN)
- Total bilirubin ≤2.5 X ULN

4.3.5 HIV infection status must be documented as either absent or present, as defined below:

Absence of HIV-1 infection, as documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit, within 30 days prior to Step 2 entry.

OR

HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to Step 2 entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen or plasma HIV-1 RNA viral load.

NOTE: The term “licensed” refers to a US FDA-approved kit, which is recommended. For sites that are unable to obtain an FDA-approved kit, a kit that has been certified or licensed by an oversight body within the country and validated internally is acceptable.

WHO and Centers for Disease Control and Prevention (CDC) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

4.3.6 For HIV-positive candidates only: CD4+ cell count of ≥50 cells/mm^3, performed within 7 days prior to entry at a DAIDS-approved laboratory.

4.3.7 For females of reproductive potential, negative serum or urine pregnancy test within 7 days prior to entry. Female participants who are participating in sexual activity that could lead to pregnancy must agree to use one reliable non-hormonal method of contraception (condoms or an IUD), or another method (diaphragm or cervical cap) if it is approved by the national regulatory authority and used according to package insert, while receiving study medications.

NOTE: Female participants who are not of reproductive potential or whose male partner/s has/have undergone successful vasectomy with documented azoospermia or has/have documented azoospermia for any other reason, are eligible without requiring the use of contraceptives. Participant-reported history is acceptable documentation of menopause (i.e., at least 1 year amenorrheic), hysterectomy, or bilateral oophorectomy or bilateral tubal ligation; these participants are all considered not of reproductive potential.

4.3.8 Willingness to be hospitalized for a minimum of 9 consecutive days.

4.3.9 Ability to produce an overnight sputum sample of sufficient quality and quantity. As a guideline, this should be 10 mL or more during a 16-hour collection period.

NOTE: If a participant’s failure to produce sufficient sputum appears to be due to poor technique rather than low volume of sputum production, this evaluation may be repeated.

4.4 Exclusion Criteria for Step 2

4.4.1 Current treatment with INH or receipt of INH during the 7 days prior to Step 2 entry.

NOTE: Participants who have been started on INH-containing anti-TB treatment and have received this treatment for less than or equal to 2 weeks, but for whom TB drugs have been discontinued because of resistance to INH (with or without resistance to RIF), can participate in the study, but may need to be hospitalized, at the discretion of the investigator, while these drugs wash out; the minimum washout period for these drugs is 7 days.

4.4.2 **Receipt of more than 7 cumulative days of second-line anti-TB drugs (including all drugs with anti-TB activity, except INH, RIF, ethambutol, pyrazinamide, and streptomycin) and/or antibiotics intended for bacterial treatment that may have anti-TB activity, including amoxicillin/clavulanate (Augmentin), linezolid, metronidazole, or drugs from the quinolone class, within the 14 days prior to Step 1 screening sputum collection. The minimum washout period for these drugs is 7 days prior to Step 2 pre-entry sputum collection.**

4.4.**3** Known exposure to a person diagnosed with XDR-TB or known personal diagnosis of XDR-TB in the past.

4.4.**4** Breastfeeding.

4.4.**5** Known allergy/sensitivity to INH.

4.4.**6** Karnofsky score <60 or poor general condition where any delay in full TB treatment cannot be tolerated in the opinion of the investigator (at screening).

4.4.**7** Any of the following co-morbidities, complications, or underlying medical conditions:

- Known current neurological TB (e.g., TB of the spine, TB meningitis)
- Peripheral neuropathy ≥Grade 2, according to the December 2004 (Clarification, August 2009) Division of AIDS (DAIDS) Toxicity Table, within 14 days prior to entry
- Current or history of epilepsy, defined as seizure disorder requiring current treatment with an antiepileptic medicine or history of any seizures within the prior year

4.4.**8** Any condition as determined by physical examination, medical history, laboratory data, or chest x-ray which, in the opinion of the investigator, would interfere with participation in the study.

4.5 Study Enrollment Procedures

4.5.1

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received. Site-specific informed consent forms (ICFs) 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.

Upon receiving final IRB/EC and any other applicable RE approvals for an amendment, 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 the 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.

Protocol activation is required prior to enrolling participants into the study. The Network Coordinating Center will provide notification of activation.

Once a candidate for study entry has been identified, details will be carefully discussed with the participant. The participant will be asked to read and sign the approved protocol consent form.

For participants from whom a signed informed consent has been obtained, an ACTG Screening Checklist must be entered through the Data Management Center (DMC) Subject Enrollment System.

4.5.2 Registration/Randomization

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure Results form must be completed and keyed into the database.

Patients who are eligible for participation in the study based on screening results will be registered to the protocol at the time of enrollment.

During Stage 1, Group 1 participants who meet Step 2 entry criteria will be randomized 1:1:1 to one of three doses of INH (5, 10, or 15 mg/kg). Group 1 participants who do not meet Step 2 entry criteria, as well as Group 2 and 3 participants will be enrolled in Step 1, but will not receive study drug. They will be discontinued from the study after their Step 1, Day 0 visit and referred for standard local TB treatment.

During Stage 2, Group 1 participants who meet Step 2 entry criteria will be randomized as during Stage 1. Group 2 participants who meet Step 2 entry criteria will be registered and assigned to receive 5 mg/kg study drug daily. **Group 3 participants who meet Step 2 entry criteria will be randomized 1:1 to receive 15 mg/kg or 20 mg/kg study drug daily.** Group 1**, 2, or 3** participants who do not meet Step 2 entry criteria will be enrolled in Step 1, but will not receive study drug. They will be discontinued from the study after their Step 1 Day 0 visit and referred for standard local TB treatment.

During Stage 2, enrollment of Group 2 participants will proceed so that, on average, for every two Group 1 participants enrolled in Step 2 per month, one Group 2 participant will be enrolled. The enrollment for Group 2 will be controlled by setting a recruitment limit, and it will be manually adjusted by the data manager and statisticians routinely (e.g., every month or twice per month).

4.6 Coenrollment Guidelines

Sites are encouraged to coenroll participants in A5243, “Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses.” Coenrollment in A5243 does not require permission from the A5312 protocol chairs. For specific questions and approval for coenrollment in other studies, sites must contact the protocol chairs via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

INH is approved for use by the US FDA for the treatment of DS-TB. The recommended dose of INH is 5 mg/kg (up to 300 mg daily) once daily for active TB. For the treatment of latent TB infection, the recommended dose is 10-15 mg/kg (up to 900 mg) twice- or thrice-weekly. In this study, INH will be given at 5 mg/kg daily to participants with DS-TB and at 5, 10, or 15 mg/kg once daily, for a total of seven daily doses, to participants infected with *M. tuberculosis* that has an *inhA* resistance mutation **or at a dose of 15 or 20 mg/kg to participants infected with *M. tuberculosis* that has a *katG* mutation.** The rationale for the higher doses is to try to overcome INH resistance by increasing the dose. In addition, participants will receive vitamin B6 ≥25 mg daily.

5.1 Regimens, Administration, and Duration

Stage 1

Step 1:
Group 1: Participants in Group 1 who do not meet Step 2 entry criteria but are enrolled for determination of MIC only will not receive study drug.

Groups 2 and 3: In Stage 1, participants infected with *M. tuberculosis* with neither *katG* nor *inhA* mutations (Group 2) and those infected with *M. tuberculosis* with a *katG* mutation with or without an *inhA* mutation (Group 3) will not receive study drugs.

Step 2:
Group 1 (n=15): Participants infected with *M. tuberculosis* with an isolated *inhA* mutation will be randomized 1:1:1 to receive the following treatments for 7 days:

5 mg cohort	INH 5 mg/kg by mouth once daily on Days 1-7 plus vitamin B6 ≥25 mg daily
10 mg cohort	INH 10 mg/kg by mouth once daily on Days 1-7 plus vitamin B6 ≥25 mg daily
15 mg cohort	INH 15 mg/kg by mouth once daily on Days 1-7 plus vitamin B6 ≥25 mg daily

Stage 2

Step 1:
Participants who do not meet Step 2 entry criteria but are enrolled only for determination of MIC will not receive study drug.

Step 2:
Group 1 (n=33): Participants infected with *M. tuberculosis* with an isolated *inhA* mutation will be randomized 1:1:1 to receive the following treatments for 7 days:

5 mg cohort	INH 5 mg/kg by mouth once daily on Days 1-7 plus vitamin B6 ≥25 mg daily
10 mg cohort	INH 10 mg/kg by mouth once daily on Days 1-7 plus vitamin B6 ≥25 mg daily
15 mg cohort	INH 15 mg/kg by mouth once daily on Days 1-7 plus vitamin B6 ≥25 mg daily

Group 2 (n=16): Participants infected with *M. tuberculosis* with neither *katG* nor *inhA* mutations who meet the Step 2 entry criteria will receive the following treatment for 7 days:

Control	INH 5 mg/kg by mouth once daily on Days 1-7 plus vitamin B6 ≥25 mg daily

Group 3 (n=20): Participants infected with *M. tuberculosis* with a *katG* mutation, with or without an *inhA* mutation, who meet the Step 2 entry criteria will receive the following treatment for 7 days:

katG 15 mg cohort	**INH 15 mg/kg by mouth once daily on Days 1-7 plus vitamin B6 ≥25 mg daily**
katG 20 mg cohort	**INH 20 mg/kg by mouth once daily on Days 1-7 plus vitamin B6 ≥25 mg daily**

INH is available in 100 mg tablets. INH will be administered orally daily in the morning on an empty stomach. Doses of INH will be given according to the weight bands outlined below:

Dose cohort	Weight	Dose
5 mg/kg	≥40 kg and ≤70 kg	300 mg
5 mg/kg	>70 kg and ≤90 kg	400 mg
10 mg/kg	≥40 kg and ≤55 kg	500 mg
10 mg/kg	>55 kg and ≤65 kg	600 mg
10 mg/kg	>65 kg and ≤75 kg	700 mg
10 mg/kg	>75 kg and ≤85 kg	800 mg
10 mg/kg	>85 kg and ≤90 kg	900 mg
15 mg/kg	≥40 kg and ≤43 kg	600 mg
15 mg/kg	>43 kg and ≤50 kg	700 mg
15 mg/kg	>50 kg and ≤57 kg	800 mg
15 mg/kg	>57 kg and ≤63 kg	900 mg
15 mg/kg	>63 kg and ≤70 kg	1000 mg
15 mg/kg	>70 kg and ≤76 kg	1100 mg
15 mg/kg	>76 kg and ≤83 kg	1200 mg
15 mg/kg	>83 kg and ≤90 kg	1300 mg
20 mg/kg	**≥40 kg and ≤43 kg**	**800 mg**
20 mg/kg	**>43 kg and ≤48 kg**	**900 mg**
20 mg/kg	**>48 kg and ≤53 kg**	**1000 mg**
20 mg/kg	**>53 kg and ≤58 kg**	**1100 mg**
20 mg/kg	**>58 kg and ≤63 kg**	**1200 mg**
20 mg/kg	**>63 kg and ≤68 kg**	**1300 mg**

Dose cohort	Weight	Dose
20 mg/kg	**>68 kg and ≤73 kg**	**1400 mg**
20 mg/kg	**>73 kg and ≤78 kg**	**1500 mg**
20 mg/kg	**>78 kg and ≤83 kg**	**1600 mg**
20 mg/kg	**>83 kg and ≤88 kg**	**1700 mg**
20 mg/kg	**>88 kg and ≤93 kg**	**1800 mg**

Participants will receive INH at the assigned dose for 7 days and then will be referred to the local/national TB program for TB treatment by Day 10 (or earlier if study treatment is prematurely discontinued). Results of study-related DST will be provided to the treatment program for their use, as appropriate.

5.2 Study Product Formulation and Preparation

INH tablets locally procured by the sites must be stored in accordance with the manufacturer's instructions and be the same strength and formulation for the duration of the study.

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

INH and vitamin B6 will be obtained locally for use by study participants.

INH will be obtained from a source matching at least one of the following qualifications:

- Approved by the U.S. FDA
- Approved by a country listed under the Federal Food, Drug, and Cosmetic Act Chapter VIII, Section 802(b) (1) (A) (These countries are Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or the countries of the European Union or country in the European Economic Area)
- Approved by and listed under the WHO Prequalification Programme (http://**extranet**.who.int/prequal/)

Each CRS conducting A5312 must obtain the approval for use of locally procured INH tablets from the protocol team prior to administration to A5312 participants and keep a detailed log of the manufacturer information (name and location), strength and dosage form, each lot number, expiration date, and start and stop dates for usage of that lot number. This is in addition to the accountability records required in section 5.3.2.

The source of vitamin B6 must also meet the requirements of this policy.

5.3.2 Study Product Accountability

The Clinical Research Site Pharmacist of Record is required to maintain records of all study products received and dispensed to study participants, and final disposition of all study products.

5.4 Concomitant Medications

Below are lists of selected concomitant medications. These lists are only current as of the date of this protocol. Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medications' and study agents' most recent package inserts, Investigator's Brochures, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the ACTG Drug Interactions Database, located at: http://tprc.pharm.buffalo.edu/home/di_search/.

5.4.1 Required Medications

TB-Drug-Induced Peripheral Neuropathy Prophylaxis
Vitamin B6 (pyridoxine) once daily while participant is receiving INH; vitamin B6 will be required and provided by the site. A dose of 25 mg is recommended but may be higher based on the current local, national, or international dosing guidelines.

5.4.2 Prohibited Medications

Use of other anti-TB medications is prohibited from screening until after the final dose of study medications. Antacids must not be given together with the study drug.

5.4.3 Precautionary Medications

For a list of precautionary medications, refer to the ACTG Drug Interactions Database (see link above).

5.5 Adherence Assessment

Study doses of INH will be observed during hospitalization, and adherence will be documented by study staff using hospital records.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Events

6.1.1 **Table 6.1-1:** Step 1

Evaluation	Screening	Step 1 Day 0[2]
Spot Sputum Collection	X	X[3]
AFB Microscopy	X	
Genotypic DST with HAIN MTBDR*plus*	X	
Culture and Phenotypic DST Determination with MIC		X
Hospitalization[1]	X	

[1]At the discretion of the investigator, some participants may be hospitalized during the screening evaluations, but this is not a requirement.
[2]The screening and Step 1 Day 0 visits may be combined for these participants.
[3]Step 1 Day 0 spot sputum collection is only required if the screening spot sputum is insufficient or inadequate for Step 1 entry evaluations.

6.1.2 **Table 6.1-2**: Step 2

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										

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	
NAT2 genotype (blood and saliva)			X										
Chest X-ray	X[2]												
Spot Sputum Collection			X[3]										
Genotypic DST (MTBDR*s*/)[4]			X										
Overnight Sputum Collection		X	X	X	X	X	X	X	X	X			
EBA Analysis by Solid Culture CFU **(Groups 1 and 2 only)** Determination and Liquid MGIT Culture for TTD[5] **(all groups)**		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.

6.2 Timing of Evaluations

6.2.1 Screening and Pre-Entry Evaluations

Screening
Screening procedures will be performed within the 2 weeks prior to entry unless otherwise noted to minimize participants' waiting time for a decision about whether or not they can be enrolled. In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database.

To avoid unnecessary delay in initiating TB treatment, screening evaluations for Step 1 and Step 2 may occur on the same day.

Recruitment will occur through the study site(s) and may include referrals of TB participants from outlying TB clinics and local or regional mycobacteriology laboratories. Participants with a presumptive diagnosis of sputum smear positive or GeneXpert-positive pulmonary TB will be invited to screen for the study.

NOTE: Some participants may be hospitalized during the screening period, at the discretion of the investigator, for the safety of the participant or to decrease risk of transmission to others.

Pre-entry
Only those participants who are expected to be enrolled in a treatment group will have this visit. At least 48 hours prior to the first dose of study medication, participants who will be enrolled in a treatment group will be admitted to the inpatient EBA unit at the study site to complete the pre-entry requirements. Two days prior to scheduled drug dosing, beginning at around 4pm ±1 hour, a 16-hour quantitative sputum collection will be performed. Participants who do not produce an overnight sputum sample of sufficient quality and quantity will be considered screen failures. However, if a participant's failure to produce sufficient sputum appears to be due to poor technique rather than low volume of sputum production, this evaluation may be repeated.

6.2.2 Entry Evaluations (Day 0)

6.2.2.1 Step 1, Day 0

Those participants registered to the study but not enrolled in a treatment group (i.e., Stages 1 or 2, Group 1 who do not meet Step 2 entry criteria; Stage 1, Groups 2 and 3; or Stage 2, Group 2 **or 3** who do not meet Step 2 entry **criteria) will** only have sputum for phenotypic DST determination with MIC at this visit. This evaluation may be performed on sputum collected at Step 1 Day 0 or sputum collected at screening. Thus, the screening and Step 1 Day 0 visits may be combined for these

participants. After this evaluation is performed, the participant will be discontinued from the study.

6.2.2.2 Step 2, Day 0

Those participants enrolled in a treatment group will remain in the hospital until Day 8. Registration/randomization will occur on the day of study entry. A 16-hour quantitative sputum collection will be performed. Participants who do not produce an overnight sputum sample of sufficient quality and quantity on Step 2 Day 0 will be discontinued from the study (see section 8.1). However, if a participant's failure to produce sufficient sputum appears to be due to poor technique rather than low volume of sputum production, this evaluation may be repeated.

6.2.3 Post-Entry Evaluations (for participants who meet Step 2 entry criteria)

Days 1-7 (Treatment)
Participants must begin treatment within 24 hours after registration/randomization. Participants will receive their assigned dose of INH in the morning on an empty stomach, defined as nothing by mouth except water and study medications 2 hours pre-dose and 1 hour post-dose.

Day 8 (Discharge)
Those participants enrolled in a treatment group will be discharged from the hospital on Day 8. Upon discharge from the hospital and no later than Day 10, participants will be referred to the standard local TB treatment.

Final Visit
This visit will occur 14 (±3) days after the final dose of study medications to evaluate for evidence of delayed toxicity and to follow up on any adverse events (AEs) that occurred during the study.

6.2.4 Discontinuation Evaluations

Evaluations for Randomized or Registered Participants Enrolled to Step 2 Who Do Not Start Study Treatment
All case report forms (CRFs) must be completed and keyed for the period up to and including Step 2 Day 0.

Evaluations for Registered Participants Not Enrolled to Step 2
All CRFs must be completed and keyed for the period up to and including Step 1 Day 0. An off-study form will be completed for these participants at Step 1 Day 0. No premature discontinuation evaluations are needed.

Premature Study Discontinuation Evaluations
If study withdrawal occurs, the participant will be asked to complete a premature discontinuation visit. Assessments to be performed at the premature discontinuation visit are listed in section 6.1. Participants who prematurely discontinue treatment will be prematurely discontinued from the study.

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS Web site for information about what must be included in the source document: **https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf**.

All stated evaluations are to be recorded on the CRF and keyed into the database unless otherwise specified. This includes events that meet the International Conference on Harmonisation (ICH) definitions for a serious AE:

- Results in death
- Life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other important medical event (may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the events listed above.

To grade diagnoses, signs and symptoms, and laboratory results, sites must refer to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification, August 2009), which can be found on the DAIDS RSC Web site: **http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.**

Step 1

6.3.1 Sputum Samples

Spot Sputum Collection
Spot sputum will be collected for the following:

AFB Microscopy
Direct microscopy for acid-fact bacilli will be performed and reported as negative, or as scanty, 1+, 2+, or 3+ positive, according to IUATLD scale.

Genotypic DST with HAIN MTBDR*plus*
Hain MTBDRplus testing for detection of INH resistance (*inhA* or *katG* mutations) and RIF resistance (*rpoB* mutations) will be performed.

Culture and Phenotypic DST Determination with MIC
Phenotypic DST for INH and RIF using the proportion method. The MIC for INH will be determined.

6.3.2 Hospitalization

At the discretion of the investigator, a participant may be hospitalized during the screening period if necessary for the safety of the participant or to decrease risk of transmission to others.

Step 2

6.3.3 Documentation of HIV Status

Section 4.3.5 provides assay requirements for HIV-1 status documentation. HIV status will not be reported on a CRF.

6.3.4 Medical History

The medical history must include all diagnoses identified by the ACTG criteria for clinical events and other diagnoses. For current criteria, refer to the appendix identified in the study CRF. Allergies to any medications and their formulations must be documented.

6.3.5 Medication History

A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history.

Table 6.3.5-1: Medication History

Category	Timeframe	Location
TB treatment	Complete history, including doses	TB Medication History CRF
ART	Within 30 days prior to entry, including doses	Antiretroviral Medication History CRF
Prescription drugs for treatment of opportunistic infections	Within 30 days prior to entry	CRF
Prescription drugs for prophylaxis of opportunistic infections	Within 30 days prior to entry	CRF
Prescription drugs (other)	Within 30 days prior to entry	CRF

Category	Timeframe	Location
Alternative therapies	Within 30 days prior to entry	Record as yes/no on CRF; if yes, record details in source document
Dietary supplements	Within 30 days prior to entry	CRF

6.3.6 Clinical Assessments

Complete Physical Examination
A complete physical examination will include at a minimum an examination of the skin, head, mouth, neck and lymph nodes; auscultation of the chest; cardiac exam; abdominal exam; examination of the lower extremities for edema. The complete physical exam will also include signs and symptoms, diagnoses, and vital signs (temperature, pulse, respiration rate, and blood pressure). Neurologic examination to evaluate for peripheral neuropathy will be performed.

Targeted Physical Examination
A targeted physical examination will include vital signs (temperature, pulse, respiration rate, and blood pressure). The targeted physical examination is to be driven by any previously identified or new signs or symptoms, including diagnoses that the participant has experienced since the last visit. Neurologic examination to evaluate for peripheral neuropathy will be performed at the final study visit or, for those who discontinue the study early, at the discontinuation visit.

Karnofsky Score
This will be recorded at screening.

Height
Height will be recorded at screening only.

Weight
Weight will be recorded at all visits, except pre-entry.

Signs and Symptoms
At entry, all grades that occurred within 7 days prior to entry must be recorded; post-entry, only signs and symptoms Grade $\geq$2 must be recorded. In addition, all signs and symptoms that lead to a change in treatment must be recorded, regardless of grade.

Diagnoses
Record all diagnoses identified by the ACTG criteria for clinical events and other diseases.

Concomitant Medications
All concomitant medications (as per section 5.4) started or stopped since the last visit must be recorded on the CRF. Alternative therapies will be recorded as a yes/no on the CRF. If yes, the details will be recorded in the source documents only.

TB Medications
On-study TB treatment: INH will be administered on Days 1-7. At each visit, record all modifications, including start/stop dates, initial doses, and participant-initiated and/or health care provider-mandated modifications, and any permanent discontinuation of study TB treatment.

Standard local TB treatment: Standard local TB treatment will start on Day 8 and no later than Day 10. Record all modifications, including start/stop dates, initial doses, participant-initiated and/or health care provider-mandated modifications, and any permanent discontinuation of TB medications.

Antiretroviral Medications
Record all modifications, including start/stop dates, initial doses, participant-initiated and/or health care provider-mandated modifications, and any temporary holds or permanent discontinuations.

6.3.7 Laboratory Evaluations

Complete Blood Count with Differential
Record all values regardless of grade for: hemoglobin, platelet count, white blood cell count, absolute neutrophil count.

Complete Blood Chemistry Profile
Record all values regardless of grade for: AST, ALT, alkaline phosphatase, total bilirubin, creatinine, potassium, and albumin.

CD4+ Count (HIV-infected participants)
For participants who are HIV-infected, a CD4+ count determination performed within 7 days prior to entry at a DAIDS-approved laboratory must be recorded.

Pregnancy Test
For women with reproductive potential: Serum or urine β-HCG. (Urine test must have a sensitivity of 15-25 mIU/mL.)

NAT2 Genotype
Both whole blood and saliva will be collected for this testing. The sample of saliva will be collected using an Oragene kit.

6.3.8 Chest X-ray

A chest x-ray will be performed at screening, unless the results of a chest x-ray performed within 14 days prior to screening are available.

6.3.9 Sputum Samples

Spot Sputum Collection
Spot sputum will be collected for the following:

Genotypic DST (MTBDR*s*/)
Among those participants with MDR-TB, Hain MTBDR*s*/ testing for detection of fluoroquinolone **and injectable TB drug resistance** will be performed.

Overnight Sputum Collection
Sputum will be collected over 16 hours each night beginning at around 4pm ±1 hour, and each participant's overnight sputum samples will be pooled in an appropriate, clean container. This sputum will be used for the following:

EBA Analysis by Solid Culture CFU Determination and Liquid MGIT Culture for TTD
Sputum will be cultured on solid media, and CFU count will be determined f**or Groups 1 and 2 only**. **For all groups d**aily TTD determination will be done, and measured in hours.

Start and stop times, total volume collected, and any interruptions in collection or temperature control problems will be recorded.

6.3.10 Pharmacokinetic Sampling

See section 10.0, Pharmacology Plan. Blood samples for study drug concentrations may be collected from an indwelling catheter, or if a catheter cannot be placed or maintained successfully, by direct venipuncture.

6.3.11 Hospitalization

At the discretion of the investigator, a participant may be hospitalized during the screening period if necessary for the safety of the participant or to decrease risk of transmission to others.

All participants will be hospitalized for pre-entry and entry visits. Those participants who are randomized to receive treatment will be hospitalized during Days 1-7 to receive treatment and will be discharged from the hospital on Day 8.

7.0 CLINICAL MANAGEMENT ISSUES

7.1 Toxicity

Only toxicities related to study medications will be considered in the toxicity management section. The grading system for drug toxicities is located in the DAIDS AE Grading Table, Version 1.0, December 2004 (Clarification, August 2009), located at the DAIDS RSC web site: **http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables**.

7.1.1 Grade 1

Study participants who develop a Grade 1 AE or toxicity may continue study medications at the discretion of the site investigator.

If participants choose to discontinue study drug, the A5312 Clinical Management Committee (actg.cmcA5312@fstrf.org) should be notified within 48 hours. The site should complete the premature discontinuation evaluations, as per section 6.1.2, within 7 days after stopping study medications.

7.1.2 Grade 2

Participants who develop a Grade 2 AE or toxicity may continue study drugs, at the discretion of the site investigator, and will be followed carefully.

If participants choose to discontinue study drug, the A5312 Clinical Management Committee should be notified within 48 hours. The site should complete the premature discontinuation evaluations, as per section 6.1.2, within 7 days after stopping study medications.

Grade 2 clinical or laboratory abnormalities that are deemed likely related to study drug will be followed to stabilization or resolution to Grade ≤1. Evaluations and the frequency of follow-up visits are at the discretion of the site investigator. The A5312 Clinical Management Committee should be notified of any requirements for continuing follow-up of toxicities beyond 7 days after stopping study medications.

7.1.3 Grade 3

Unless the site investigator has compelling evidence that the Grade 3 AE or toxicity is not related to the study drug, the participant must permanently discontinue the study drug. The A5312 Clinical Management Committee should be notified within 48 hours. The site should complete the premature discontinuation evaluations, as per section 6.1.2, within 7 days after stopping study medications.

Clinical or laboratory abnormalities of Grade 3 that are deemed likely related to study medication will be followed to stabilization, resolution to Grade ≤1, or return to baseline. Evaluations and the frequency of follow-up visits are at the discretion of the site investigator. The A5312 Clinical Management Committee should be notified of any requirements for continuing follow-up of toxicities beyond 7 days after stopping study medications.

7.1.4 Grade 4

Any participant with Grade 4 toxicity will be immediately and permanently discontinued from the study. The site should complete the premature discontinuation evaluations, as per section 6.1.2, within 7 days after stopping study medications.

Clinical or laboratory abnormalities of Grade 4 that are deemed likely related to study medication will be followed to stabilization, resolution to Grade ≤1, or return to baseline. Evaluations and the frequency of follow-up visits are at the discretion of the site investigator. The A5312 Clinical Management Committee should be notified of any requirements for continuing follow-up of toxicities beyond 7 days after stopping study medications.

7.2 Other Diseases

Participants who develop new medical diagnoses during the study will be counseled and given recommendations for referrals to medical providers, as necessary.

7.3 Pregnancy

After study entry, female participants who become pregnant must immediately discontinue study treatment and complete the premature study discontinuation evaluations. They will be referred to their local clinic for standard TB care and prenatal care. Site personnel must notify the A5312 Clinical Management Committee (actg.cmca5312@fstrf.org) within 48 hours after receiving this information. Pregnancy outcomes will not be recorded.

8.0 CRITERIA FOR DISCONTINUATION

8.1 Premature Study Discontinuation

- Inability to produce an overnight sputum sample of sufficient quality and quantity over a 16-hour collection period on Step 2 Day 0
- Grade ≥3 drug-related AE or toxicity or any Grade 4 AE or toxicity (see section 7.1 Toxicity)
- Requirement for prohibited concomitant medications (see section 5.4)
- Failure by the participant to comply with inpatient hospital stay
- Pregnancy

- Nonadherence with one or more doses of study treatment
- Development of another medical condition that makes the administration of one or more planned doses of study drug inadvisable
- Inability to provide a study-required sputum sample at any time through day 8
- Request by the participant to stop study treatment or withdraw
- It is the investigator's judgment that it is no longer in the best interest of the participant to continue study participation.
- At the discretion of the ACTG, IRB/EC, NIAID, Office for Human Research Protections (OHRP), or other government agencies as part of their duties, or the investigator.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a two-stage, two-step, phase IIa, open-label EBA and PK study in participants with sputum smear-positive pulmonary TB.

No study drug is administered under Step 1. Data collected in Step 1: (a) determine eligibility to Step 2, and (b) allow characterization of INH MICs in 3 groups (secondary objective). Groups 1, 2, and 3 consist of participants infected with TB with *inhA* mutations, with DS-TB, and with TB with *katG* (with or without an *inhA* mutation) resistance-conferring mutations, respectively.

The study's primary objectives are addressed via Step 2 evaluations, through which the study estimates the 7-day EBA of INH among participants infected with TB with *inhA* mutations (Group 1) taking one of three doses of INH (5, 10, or 15 mg/kg)**, participants infected with TB with *katG* with or without *inhA* mutations (Group 3) taking 15 or 20 mg/kg of INH (TTP only),** and participants infected with DS-TB (Group 2) taking standard-dose INH (5 mg/kg daily). In addition, the association between PK parameters, such as AUC/MIC, and the EBA of INH will be examined. The total sample size for determination of participant-specific EBAs is set to **84** evaluable participants at minimum.

The study will be conducted in two stages: Stage 1 is a feasibility pilot to ensure that recruitment can proceed at a reasonable pace and also to examine whether the estimate of SDs for the sample size calculations are reasonable. During Stage 1, 15 Group 1 participants will be enrolled to Step 2, and they will be randomized 1:1:1 to a dose of 5, 10, or 15 mg/kg of INH daily. During Stage 2, 33 additional participants in Group 1 will be randomized 1:1:1 to 5, 10, or 15 mg/kg until the accrual target of evaluable participants is reached.

During Stage 1, which closed to accrual on March 26, 2015, 44 Group 2 participants enrolled to Step 1 only; these participants did not receive any study drug, but had sputum collected for MIC determination. During Stage 2, 16 participants in Group 2 who meet the Step 2 entry criteria will enter Step 2 and will be assigned to receive 5 mg/kg

daily (positive control). In addition, if the accrual target for Group 2, "Step 1 only" has not yet been met and the Group 2 participant does not meet Step 2 eligibility criteria, they may also enroll to Step 1. **During Stage 2, 20 participants in Group 3 who meet the Step 2 entry criteria will enter Step 2 and will be randomized 1:1 to receive 15 or 20 mg/kg of INH daily. In addition, if the accrual target for Group 3 "Step 1 only" has not yet been met and Group 3 participants do not meet Step 2 eligibility criteria, they may also enroll to Step 1.**

During Stages 1 and 2 combined, the maximum number of participants in Groups 1, 2, and 3 enrolling to **Step 1 only are** 70, 64, and **84**, respectively.

9.2 Endpoints

9.2.1 Primary Endpoints

9.2.1.1 Daily decline in $\log_{10}$ CFU per mL sputum from baseline to Day 7 of study treatment, defined as $EBA_{0\text{-}7}$ (CFU) = [baseline $\log_{10}$ CFU per mL (mean of the pre-entry visit and entry visit sputum colony counts) – Day 7 $\log_{10}$ CFU per mL]/7 (**Groups 1 and 2**)

9.2.1.2 Daily decline in TTD from baseline to Day 7 of study treatment, defined as $EBA_{0\text{-}7}$ (TTD) = [baseline TTD (mean of the pre-entry visit and entry visit TTDs) – Day 7 TTD]/7 (**all groups**).

9.2.1.3 Daily $\log_{10}$ CFU per mL sputum and TTD from baseline to Day 7 of study treatment; area under the time-concentration curve (AUC) for INH; MIC of *M. tuberculosis* isolates against INH (Group 1 **for CFU and TTD and Group 3 for TTD only**)

9.2.1.4 Grade 2 or higher drug-related adverse clinical or laboratory events (**all groups**)

9.2.2 Secondary Endpoints

9.2.2.1 Steady state PK parameters, including maximum concentration (C_{max}), $AUC_{0\text{-}24}$, and $T_{1/2}$; NAT2 acetylator status (See Section 10.0) (**all groups**). All PK parameters will be measured from the PK sampling at Day 6 and NAT2 acetylator status will be determined based on specimens collected at Step 2 Day 0.

9.2.2.2 INH MIC against *M. tuberculosis* isolates as determined by phenotypic DST (all groups). INH MIC will be determined from spot sputum collected at Step 1 Day 0.

9.2.2.3 AUC/MICs which reach 50% of the mean $EBA_{0\text{-}7}$ (CFU) and $EBA_{0\text{-}7}$ (TTD) among Group 2 participants (Group 1 **for CFU and TTD and Group 3 for TTD only**). INH MIC will be determined from spot sputum

collected at Step 1 Day 0 and AUC will be measured from the PK sampling at Day 6.

9.2.2.4 The endpoints below are created separately based on log_{10} CFU and TTD.

If the number of phases is the same for every dosing **cohort:**

- EBA measured by early- and late-phase individual-based parameter estimates from nonlinear mixed effect models. The early- and late-phase slopes are denoted as $EBA_{0\text{-}2}$ and $EBA_{2\text{-}7}$, respectively. Before fitting the model, both TTDs and log_{10} CFU from the pre-evaluation and entry visits will be averaged and treated as the baseline TTD and log_{10} CFU (**all groups**).

If the number of phases differs between every dosing **cohort**:

- EBA measured by individual-based parameter estimates from linear or nonlinear mixed effect models. Before fitting the model, both TTDs and log_{10} CFU from the pre-evaluation and entry visits will be averaged and treated as the baseline TTD and log_{10} CFU.
- (log_{10} CFU only) EBA measured by ratio of the following areas: numerator = AUC of observed log_{10} CFU over 7 days and denominator = baseline log_{10} CFU for each **participant.**

9.2.3 Exploratory Endpoints

9.2.3.1 Daily TTD and log_{10} CFU per mL sputum between baseline and Day 7. Both TTDs and log_{10} CFU from the pre-evaluation and entry visits will be averaged and treated as the baseline TTD and log_{10} CFU.

9.2.3.2 NAT2 genotype results from the new PCR method using saliva sample; NAT2 genotype results from standard methods that use sequencing using whole blood sample. NAT2 acetylator status will be determined based on specimens collected at Step 2 Day 0.

9.2.3.3 MTBDR*s*/ result (i.e., binary resistance status of quinolone **and aminoglycoside**) based on sputum collected at Step 2 Day 0.

9.3 Randomization and Stratification

No randomization takes place under Step 1. Participants in Group**s** 1 **and 3** who are eligible for Step 2 will be randomized equally to the three **and two** doses**, respectively**. During Stage 2, participants in Group 2 who are eligible for Step 2 will be enrolled at a pace to try to keep enrollments into each dosing cohort about equal (on average enroll two Group 1 participants into Step 2, then one Group 2 participant into Step 2, etc.) by setting a recruitment limit for Group 2. The data manager and statisticians will manually adjust the limit routinely (e.g., every month or twice per month). Randomization will not be stratified.

9.4 Sample Size and Accrual

Primary Objectives:

One of the primary objective**s** is to estimate the distribution of the $EBA_{0\text{-}7}$ (CFU) from each cohort in Group 1 (5, 10, and 15 mg/kg of INH for participants with an *inhA* mutation) and the $EBA_{0\text{-}7}$ (CFU) from Group 2 (5 mg/kg of INH for participants without *katG* or *inhA* mutations). **Another primary objective is to estimate the distribution of the $EBA_{0\text{-}7}$ (TTP) from each cohort in Group 1, Group 2, and each cohort in Group 3.** The aim is to establish proof-of-concept for the higher doses of INH.

Sample Size:

The planned sample size is 16 participants per treatment **cohort in Group 1 and Group 2**; participants discontinuing before the day 7 sample collection will be replaced. This sample size is similar to that of other recent exploratory EBA studies.

Here is some information about the likely precision of estimates that can be achieved with the planned sample size of 16 participants in this proof-of-concept study. Among participants with DS-TB who were taking 300 mg doses of INH, the estimated mean $EBA_{0\text{-}5}$ was 0.21 $\log_{10}$CFU/mL/day (n=16, SE 0.03, between-participant SD 0.12, coefficient of variation [CV] 57%) [**41**]. We assume the mean $EBA_{0\text{-}7}$ (CFU) from Group 1 is approximately half of $EBA_{0\text{-}7}$ (CFU) from Group 2. Further assuming constant CV, the table below gives the anticipated precisions (half-widths) of 95% confidence intervals (CIs) around estimates of $\log_{10}$CFU/mL/day for any one Group 1 cohort and for the Group 2 cohort, for sample sizes of 10, 16, and 20. Because the MIC distribution may be more variable for Group 1, the table also shows anticipated CI widths for a Group 1 cohort if the CV and SD are larger (114% and 0.120, respectively).

Table 9.4-1: Sample Size per Arm and Expected Half-width of 95% CI for the Hypothesized Mean Log_{10} CFU/mL Decrease per Day with a Range of Estimated CV and SD

Group	Sample Size per Group	Hypothesized Mean log_{10}CFU/mL/day	CV	SD	Expected Half-width of 95% CI
Any one Group 1 cohort	10	0.105	57%	0.060	0.043
	16	0.105	57%	0.060	0.032
	20	0.105	57%	0.060	0.028
Any one Group 1 cohort	10	0.105	114%	0.120	0.086
	16	0.105	114%	0.120	0.064
	20	0.105	114%	0.120	0.056
Group 2	10	0.210	57%	0.120	0.086
	16	0.210	57%	0.120	0.064
	20	0.210	57%	0.120	0.056

For Group 1 cohorts, the sample size of 16 is required for a two-sided 95% CI with a precision (half-width) of less than or equal to 0.064 with SDs between 0.060 and 0.120. This means that, for example, if the mean of EBA_{0-7} (CFU) from the 15 mg/kg of INH for participants with an *inhA* mutation is 0.1 and the SD is 0.12, there is 95% probability that the CI of 0.04 and 0.17 covers the true mean.

Similarly, if the mean of EBA_{0-7} (CFU) from Group 2 is 0.2 and the SD is 0.12, there is 95% probability that the CI of 0.14 and 0.26 covers the true mean.

This sample size should allow for evaluation of the association between AUC/MIC and EBA_{0-7}, one of the other primary analyses, with high precision, as the data from all experimental dosing cohorts will be pooled for this PK/PD analysis [9, 13, 15, **42**].

For Group 3, the sample size of 10 per dosing cohort was selected since the analysis of EBA_{0-7} (TTP) per dosing cohort will be exploratory. Assuming the SD for Group 3 cohorts will be 6, which is the overall SD of EBA_{0-14} (TTP) from the previous ACTG EBA study (A5307, unpublished), a half-width of a 95% CI is 0.086 with the sample size of 10. This means, for example, if the mean of EBA_{0-7} (TTP) from a dosing cohort in Group 3 is 13, there is 95% probability that the CI of 9.28 and 16.7 covers the true mean. A possible dosing effect for this group will be examined through visual displays.

Accrual:
During Stage 1, five participants were recruited to each cohort in Group 1. During Stage 2, 11 additional participants will be recruited to each cohort in Group 1, **20 participants in Group 3,** and 16 participants in Group 2 will be recruited. In the final analyses, the data from both stages will be combined. The time to accrual for this study (Stage 1 and 2 combined) is approximately **4** years.

To maintain desired precision of estimation (primary analyses), participants who discontinue the study prior to the Day 7 evaluations will be replaced. All data from every randomized participant will be stored in the study database, and will be examined for the final analyses.

Participants enrolling to Step 1 only will be considered evaluable if all data that are required are available at screening and/or entry regardless of subsequent known or unknown loss to follow up.

Table 9.4-2: A5312 Accrual Targets

	Resistance Mutation	Participants Completing Step 1 Only[1]	Participants Completing Step 1 and Step 2[2]		Total Participants
		Stage 1 & Stage 2 Combined	Stage 1	Stage 2	
Group 1	*inhA*	Minimum of 16 to a maximum of 70[3]	15 (5 per dosing cohort)	33 (11 per dosing cohort)	Step 1 only: maximum of 70[3] Steps 1 and 2: 48
Group 2	Neither *inhA* nor *katG*	Minimum of 48 to a maximum of 64[4]	-	16	Step 1 only: maximum of 64[4] Steps 1 and 2: 16
Group 3	*katG* with or without *inhA*	**Minimum of 64 to maximum of 84**	**-**	**20 (10 per dosing cohort)**	**Step 1 only: maximum of 84[5] Steps 1 and 2: 20**

[1] Participants completing Step 1 only (participants who were considered for Step 2 but could not enter Step 2, or participants who were considered for Step 1 only) will provide sputum for determination of MIC distribution, and then be discontinued from the study.
[2] Participants completing Step 1 and Step 2 will provide sputum for determination of MIC distribution and participate in the treatment part of the study.
[3] Once the Group 1 accrual target is reached for participants completing Steps 1 and 2, accrual beyond the minimum for those completing Step 1 only will stop.
[4] Once the Group 2 accrual target is reached for participants completing Steps 1 and 2, accrual beyond the minimum for those completing Step 1 only will stop.
[5] Once the Group 3 accrual target is reached for participants completing Steps 1 and 2, accrual beyond the minimum for those completing Step 1 only will stop.

9.5 Monitoring

Accrual reports will be created and distributed to the protocol team periodically (e.g., once a month) to ensure that the total target number of evaluable participants is enrolled. The report will include information such as screening, accrual, and retention. **The first Tuberculosis Transformative Science Group (TB TSG) Study Monitoring Committee (SMC) review took place 6 months after the study opening, and feasibility of this study was reviewed.**

At the second SMC review, the TB TSG SMC **reviewed** the SDs of the $EBA_{0\text{-}7}$ (CFU) among participants in Group 1 to evaluate if the estimates of SDs used for the sample size calculations **were** reasonable (i.e., the SD of the $EBA_{0\text{-}7}$ (CFU) from Group 1 varies between 0.06 and 0.12). If the SD from each cohort in Group 1 **was** larger than expected, the sample size **could have been** increased up to 22 per cohort, to improve the precision of 95% CIs around mean $EBA_{0\text{-}7}$ (CFU) for Group 1 cohorts. With the increased sample size of 22, a half-width will be reduced to less than or equal to 0.053 with SDs between 0.060 and 0.120. **However, the SMC determined the sample size increase from 16 to 22 in Group 1 cohorts was not necessary.**

During the study, the safety and tolerability of the study medication will be monitored by means of adverse event reports (AER) and toxicity reports presenting laboratory and clinical data. The report will be stratified by group, and within Group 1, by dose. It is required that these data be entered into the database within two business days of the time at which the results of the laboratory tests or clinical examinations become available. The study team will discuss these reports on regularly scheduled conference calls or by e-mail and any concerns will be presented to the TB TSG SMC. The TB TSG SMC will also review the DAIDS Safety Monitoring Report every 3 months.

9.6 Analyses

9.6.1 Analyses of Primary Endpoints

9.6.1.1
Descriptive statistics of $EBA_{0\text{-}7}$ (CFU) for each of **the cohorts in Groups 1 and 2 will** be reported in a table. Box plots and a plot with four CIs will be created.

9.6.1.2
Descriptive statistics of $EBA_{0\text{-}7}$ (TTD) for **each of the cohorts will** be reported in a table. Box plots and a plot with **six** CIs will be created.

9.6.1.3
The relationship between the AUC/MIC and the EBA will be evaluated with linear or nonlinear models, adjusting for other covariates, such as baseline $\log_{10}$ CFU per mL. PK/PD modeling will be performed to evaluate the relationship between drug concentrations and rate or magnitude of bacterial decline. The distributions of PK/PD parameters will be examined first and appropriate transformations will be applied if necessary.

9.6.1.4 Grade 2 or higher AEs will be reported in a tabular form by **cohorts**.

9.6.2 Analyses of Secondary Endpoints

9.6.2.1 INH PK parameters will be estimated using noncompartmental analysis and the descriptive statistics will be reported by NAT2 genotype status (See section 10.0).

9.6.2.2 The distribution of INH MIC against *M. tuberculosis* isolates with *inhA* mutation, *katG* mutation, or neither of these mutations will be reported.

9.6.2.3 The AUC/MIC that achieves 50% of the mean EBA in Group 2 will be estimated and designated the "Target AUC/MIC". A Monte Carlo simulation will be performed using the MIC distribution (Group 1), NAT2 genotype distribution (Groups 1 and 2), and distribution of AUC values (Groups 1 and 2) associated with each dose and put to estimate the proportion of participants who have TB with an *inhA* mutation in a population would be expected to achieve the target AUC/MIC with 5, 10, or 15 mg/kg daily. **As exploratory analysis, the same analysis will be performed for Group 3 to determine which proportion of individuals with TB with a *katG* mutation would be expected to achieve the target AUC/MIC with a dose of 15 or 20 mg/kg daily.**

9.6.2.4 The same analysis below will be conducted separately based on $\log_{10}$ CFU and TTD. If the number of phases is the same for every dosing **cohort**:

- **Six** bi-exponential models **for $\log_{10}$ CFU and four bi-exponential models** will be fit in order to estimate the "early" and "late" phase slopes for each **cohort**. Since this is an INH mono-therapy study, there may be an inflection point at Day 2 after the initiation of INH treatment.

If the number of phases is not the same for every dosing **cohort:**

- **Six** linear or nonlinear mixed effect models **for $\log_{10}$ CFU and four linear or nonlinear mixed effect models for TTD** will be fit in order to estimate treatment effect for each **cohort**.
- (For $\log_{10}$ CFU only): Another approach will be taken to utilize the area between baseline CFU per mL and the CFU curve (ABBCC) for each participant, as measured using the trapezoidal rule. Since baseline CFU per mL may differ substantially between **groups**, the ABBCC will be expressed as a proportion of the total area under the baseline CFU per mL. The descriptive statistics will be reported **for each cohort.**

9.6.3 Analyses of Exploratory Endpoints

9.6.3.1 Daily $\log_{10}$ CFU will be plotted against daily TTD and the correlation between these outcomes will be evaluated.

9.6.3.2 The ability of the saliva test to accurately characterize acetylator status (fast, intermediate, or slow) as determined by sequencing (gold standard) will be evaluated.

9.6.3.3 Prevalence of quinolone **and aminoglycoside resistance** will be reported in a table.

10.0 PHARMACOLOGY PLAN

10.1 Pharmacology Objectives

See sections 1.2.2 and 1.3.1.

10.2 Pharmacology Study Design

10.2.1 Methods and Timing for Assessing, Recording, and Analyzing PK Outcome Measures

Intensive PK sampling will be performed on Day 6 of Step 2 when INH is at steady state, with blood collected pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose. **PK samples are to be collected at the specified time points within the allowed applicable window periods as follows—pre-dose: 0-10 minutes before dose; 0.5 hours to 8 hours post-dose: ±10 minutes of dosing time; 12 hours and 24 hours post-dose: ±15 minutes of dosing time and prior to next dose.** The INH MIC for *M. tuberculosis* for each individual will be determined and AUC/MIC for each study participant will be estimated, as this is the PD parameter that correlates best with efficacy for this drug against *M. tuberculosis*.

10.2.2 PK Evaluations

PK parameters for INH will be derived from plasma concentration versus time data. Samples will be drawn on a specified study day at optimized sampling times, as per section 10.2.1. The PK parameters to be assessed include:

- AUC_{0-24} – area under the plasma concentration-time curve in one dosing interval over 24 hours;
- C_{max} – maximum observed plasma concentration;
- C_{min} – minimum observed plasma concentration;
- T_{max} – time of maximum observed plasma concentration;
- $T_{1/2}$ – elimination half-life; and
- CL/F – oral clearance.

Individual participant PK parameter values will be derived by noncompartmental methods using a validated PK program. In addition, PK/PD modeling will be performed to evaluate the relationship between drug concentrations and rate or magnitude of bacterial decline. Dates, times, amounts, and fasted/fed status for the last three INH doses will be collected on CRFs. Fasted is defined as nothing by mouth except water and study medications 2 hours pre-dose and 1 hour post-dose. In addition, information that could explain unusual PK values (e.g., vomiting after the dose, not fasting when taken) or reasons for a missed sample (e.g., dropped tube, IV stopped working) are to be reported.

10.2.3 Pharmacogenomics: Host Genetic Analysis

NAT2 genotyping will be performed to determine acetylator status (fast, medium, or slow) and will be used as an explanatory variable in PK analyses.

10.2.4 Pharmacokinetics: Blood Collection and Processing

Blood samples for study drug concentrations will be collected from an indwelling catheter, or, if a catheter cannot be placed successfully, by direct venipuncture. If a catheter is used for blood collection, then prior to blood sampling, the fluid in the catheter will be completely withdrawn at each sampling time and discarded. Each sample will require approximately 4 mL of blood be drawn into one Vacutainer tube.

10.2.5 Sample Processing and Storage

Detailed blood processing, handling, and storage procedures can be found in the A5312 Laboratory Processing Chart (LPC).

Plasma samples will be processed and frozen immediately in an upright position at -70ºC or colder, in storage boxes. These samples will be used only for PK studies. They will be stored frozen until study completion. During frozen storage, samples will be labeled with coded sample and volunteer identifiers, and not with name.

10.2.6 Laboratory Performing the Assays

Plasma INH concentrations will be determined by a validated high-performance liquid chromatography procedure performed according to written standard operating procedures. The intraday accuracy and intraday precision will be obtained with quality control samples, which will be analyzed concurrently with each set of volunteer samples. Quality control procedures will be in place to ensure stability of sample materials.

10.3 Primary and Secondary Data, Modeling, and Data Analysis

Refer to section 10.2.2 for definitions of AUC, C_{max}, CL/F, T_{max}, and $T_{1/2}$ for this analysis.

Data will initially be analyzed using noncompartmental methods. The C_{max}, T_{max}, and C_{min} will be determined for each participant by inspection of the serum concentration-versus-time graphs. The AUC from time zero to the time of the last quantifiable concentration (AUC_{0-t}) will be determined by the linear trapezoidal rule.

PK/PD modeling will be performed to evaluate the relationship between drug concentrations and rate or magnitude of bacterial decline. A detailed plan of PK and PK/PD data analysis is included in the Statistical Analysis Plan.

10.4 Anticipated Outcomes

See Hypothesis 1.1.1.

NAT2 acetylator status will explain a large proportion of the variability in INH PK estimates.

11.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1 Records to Be Kept

CRFs will be provided for each participant. Participants must not be identified by name on any CRFs. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon randomization.

11.2 Role of Data Management

11.2.1 Instructions concerning the recording of study data on CRFs will be provided by the ACTG DMC. Each clinical research site is responsible for keying the data in a timely fashion.

11.2.2 It is the responsibility of the ACTG DMC to assure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

11.3 Clinical Site Monitoring and Record Availability

11.3.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual participant records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to

ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

11.3.2 The site investigator will make study documents (e.g., consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB/EC, the site monitors, the NIAID, the OHRP, and **other local, U.S., and international regulatory entities** for confirmation of the study data.

11.4 Expedited Adverse Event Reporting to DAIDS

11.4.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at **http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual**.

The DAIDS Adverse Events Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-**ES (now part of the NIAID Clinical Research Management System) at CRMSsupport@niaid.nih.gov.** Site queries may also be sent from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website at **http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting**. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

11.4.2 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.

The study agent for which expedited reporting is required is **isoniazid**.
In addition to the EAE Reporting Category identified above, other AEs that must be reported in an expedited manner are all hepatic failures.

11.4.3 Grading Severity of Events
The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) Version 1.0 - December 2004 (Clarification dated August 2009) is used for this study and is available on the RSC website at **http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.**

11.4.4 Expedited AE Reporting Period

The expedited AE reporting period for this study is as per the EAE manual.

After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs), as defined in Version 2.0 of the EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

12.0 PARTICIPANTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent documents (Appendix I, Appendix II, Appendix III) and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight of the study. A signed consent form will be obtained from the participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, and this fact will be documented in the participant's record.

12.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by ACTG, IRB/EC, the NIAID, the OHRP, or **other local, U.S., and international regulatory entities** as part of their duties.

12.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, the NIAID, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

13.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies.

14.0 BIOHAZARD CONTAINMENT

Transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood, and blood products. Respiratory pathogens such as *Mycobacterium* tuberculosis (MTB) are transmitted by inhalation of droplet nuclei. Appropriate blood, secretion, and respiratory precautions will be employed by all personnel in the collection of clinical samples and the shipping and handling of all clinical samples and isolates for this study, as currently recommended by the Centers for Disease Control and Prevention (CDC) in the United States and the World Health Organization (WHO) internationally.

All protocol 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.

Refer to individual carrier guidelines (e.g., Federal Express or Airborne) for specific instructions and to the ACTG/IMPAACT Laboratory Technologists Committee Guidelines for Shipment and Receipt of Category A Infectious Substances and Category B Biological Substances Shipments and Instructions for Overnight Shipments documents at: http://www.hanc.info/labs/labresources/procedures/Pages/actnShippingDemo.aspx

Infection control for active TB cases and good laboratory practices for MTB isolation and storage of *Mycobacterium* isolates will be according to ACTG/IMPAACT policies and procedures, CDC/WHO guidance, and local policies and practices to minimize TB transmission.

15.0 REFERENCES

1. World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. WHO/HTM/TB/2010.3.
2. Mitnick CD, Castro KG, Harrington M, Sacks LV, Burman W. Randomized trials to optimize treatment of multidrug-resistant tuberculosis. PLoS Med 2007;4(11):e292.
3. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med 2009;360(23):2397-405.
4. World Health Organization. Treatment of tuberculosis guidelines. 4th edition. WHO/HTM/TB/2009.420.
5. Nolan CM, Goldberg SV. Treatment of isoniazid-resistant tuberculosis with isoniazid, rifampin, ethambutol, and pyrazinamide for 6 months. Int J Tuberc Lung Dis 2002;6(11):952-8.
6. Warren RM, Streicher EM, Gey van Pittius NC, et al. The clinical relevance of Mycobacterial pharmacogenetics. Tuberculosis (Edinb) 2009;89(3):199-202.
7. Donald PR, Sirgel FA, Botha FJ, et al. The early bactericidal activity of isoniazid related to its dose size in pulmonary tuberculosis. Am J Respir Crit Care Med 1997;156(3 Pt 1):895-900.
8. Schaaf HS, Marais BJ, Hesseling AC, Gie RP, Beyers N, Donald PR. Childhood drug-resistant tuberculosis in the Western Cape Province of South Africa. Acta Paediatr 2006;95(5):523-8.
9. Wilkins JJ, Langdon G, McIlleron H, Pillai GC, Smith PJ, Simonsson US. Variability in the population pharmacokinetics of isoniazid in South African tuberculosis patients. Br J Clin Pharmacol 2011;72(1):51-62.
10. Gumbo T, Louie A, Liu W, et al. Isoniazid bactericidal activity and resistance emergence: integrating pharmacodynamics and pharmacogenomics to predict efficacy in different ethnic populations. Antimicrob Agents Chemother 2007;51(7):2329-36.
11. Jayaram R, Shandil RK, Gaonkar S, et al. Isoniazid pharmacokinetics-pharmacodynamics in an aerosol infection model of tuberculosis. Antimicrob Agents Chemother 2004;48(8):2951-7.
12. Cynamon MH, Zhang Y, Harpster T, Cheng S, DeStefano MS. High-dose isoniazid therapy for isoniazid-resistant murine Mycobacterium tuberculosis infection. Antimicrob Agents Chemother 1999;43(12):2922-4.
13. Donald PR, Parkin DP, Seifart HI, et al. The influence of dose and N-acetyltransferase-2 (NAT2) genotype and phenotype on the pharmacokinetics and pharmacodynamics of isoniazid. Eur J Clin Pharmacol 2007;63(7):633-9.
14. Vilcheze C, Jacobs WR,Jr. The mechanism of isoniazid killing: clarity through the scope of genetics. Annu Rev Microbiol 2007;61:35-50.

15. Schaaf HS, Victor TC, Engelke E, et al. Minimal inhibitory concentration of isoniazid in isoniazid-resistant Mycobacterium tuberculosis isolates from children. Eur J Clin Microbiol Infect Dis 2007;26(3):203-5.
16. Abate G, Hoffner SE, Thomsen VO, Miorner H. Characterization of isoniazid-resistant strains of Mycobacterium tuberculosis on the basis of phenotypic properties and mutations in katG. Eur J Clin Microbiol Infect Dis 2001;20(5):329-33.
17. Kinzig-Schippers M, Tomalik-Scharte D, Jetter A, et al. Should we use N-acetyltransferase type 2 genotyping to personalize isoniazid doses? Antimicrob Agents Chemother 2005;49(5):1733-8.
18. Kubota R, Ohno M, Hasunuma T, Iijima H, Azuma J. Dose-escalation study of isoniazid in healthy volunteers with the rapid acetylator genotype of arylamine N-acetyltransferase 2. Eur J Clin Pharmacol 2007;63(10):927-33.
19. Selkon JB, Devadatta S, Kulkarni KG, et al. The emergence of isoniazid-resistant cultures in patients with pulmonary tuberculosis during treatment with isoniazid alone or isoniazid plus pas. Bull World Health Organ 1964;31:273-94.
20. Van Deun A, Maug AK, Salim MA, et al. Short, Highly Effective and Inexpensive Standardized Treatment of Multidrug-resistant Tuberculosis. Am J Respir Crit Care Med 2010;182(5):684-92.
21. **Reider HL, Van Deun A. Rationale for high-dose isoniazid in the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2017;21:123-4.**
22. **Kuaban C, Noeske J, Rieder HL, Ait-Khaled N, Abena Foe JL, Trebucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. Int J Tuberc Lung Dis 2015;19:517-24.**
23. **Piubello A, Harouna SH, Souleymane MB. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. Int J Tuberc Lung Dis 2014;18:1188-94.**
24. Katiyar SK, Bihari S, Prakash S, Mamtani M, Kulkarni H. A randomised controlled trial of high-dose isoniazid adjuvant therapy for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2008;12(2):139-45.
25. van der Watt JJ, Harrison TB, Benatar M, Heckmann JM. Polyneuropathy, anti-tuberculosis treatment and the role of pyridoxine in the HIV/AIDS era: a systematic review. Int J Tuberc Lung Dis 2011;15(6):722-8.
26. Petty TL, Mitchell RS. Successful treatment of advanced isonizid- and streptomycin-resistant pulmonary tuberculosis with ethionamide, pyrazinamide, and isoniazid. Am Rev Respir Dis 1962;86:503-12.
27. The results from twelve to thirty-six months in patients submitted to two studies of primary chemotherapy for pulmonary tuberculosis in East Africa. Tubercle 1969;50(3):233-56.
28. **Donald PR, Schoeman JF, Van Zyl LE, et al. Intensive short course chemotherapy in the management of tuberculous meningitis. Int J Tuberc Lung Dis. 1998;2(9):704-11.**

29. Girling DJ, The hepatic toxicity of antituberculosis regimens containing isoniazid, rifampicin and pyrazinamide. Tubercle. 1978;59(1):13-32.

30. **Trébucq A, Schweobel V, Kashongwe Z, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. Int J Tuberc Lung Dis 2018;22:17-25.**

31. World Health Organization. WHO treatment guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis. WHO/CDS/TB/2018.7.

32. Peloquin CA, Namdar R, Dodge AA, Nix DE. Pharmacokinetics of isoniazid under fasting conditions, with food, and with antacids. Int J Tuberc Lung Dis. 1999;3(8):703-10.

33. Ellard GA. The potential clinical significance of the isoniazid acetylator phenotype in the treatment of pulmonary tuberculosis. Tubercle 1984;65(3):211-27.

34. Baciewicz AM, Self TH. Isoniazid interactions. South Med J. 1985;78(6):714-8.

35. Kay L, Kampmann JP, Svendsen TL, et al. Influence of rifampicin and isoniazid on the kinetics of phenytoin. Br J Clin Pharmacol. 1985;20(4):323-6.

36. Ling DI, Zwerling AA, Pai M. Rapid diagnosis of drug-resistant TB using line probe assays: from evidence to policy. Expert Rev Respir Med 2008;2(5):583-8.

37. World Health Organization. Molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis (MDR-TB). Policy statement. 2008.

38. Diacon AH, Dawson R, Hanekom M, et al. Early bactericidal activity and pharmacokinetics of PA-824 in smear-positive tuberculosis patients. Antimicrob Agents Chemother 2010;54(8):3402-7.

39. Diacon AH, Patientia RF, Venter A, et al. Early bactericidal activity of high-dose rifampin in patients with pulmonary tuberculosis evidenced by positive sputum smears. Antimicrob Agents Chemother 2007;51(8):2994-6.

40. Rustomjee R, Diacon AH, Allen J, et al. Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. Antimicrob Agents Chemother 2008;52(8):2831-5.

41. Hafner R, Cohn JA, Wright DJ, et al. Early bactericidal activity of isoniazid in pulmonary tuberculosis. Optimization of methodology. The DATRI 008 Study Group. Am J Respir Crit Care Med 1997;156(3 Pt 1):918-23.

42. Donald PR, Diacon AH. The early bactericidal activity of anti-tuberculosis drugs: a literature review. Tuberculosis (Edinb) 2008;88 Suppl 1:S75-83.

APPENDIX I: SAMPLE INFORMED CONSENT FOR PROTOCOL A5312, STAGE 1

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)

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

INTRODUCTION

You are being asked to take part in this research study because you have pulmonary tuberculosis (TB), a bacterial infection in your lungs. This research study is conducted by the AIDS Clinical Trials Group (ACTG), which is a research organization based in the United States. Although the name contains the word “AIDS”, this study is not about research on AIDS or HIV. This study is sponsored by the United States National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Isoniazid (INH) is a drug commonly used to treat TB worldwide. Sometimes, the bacteria that cause TB can become resistant to INH. Resistance means that bacteria have adapted to a drug and are able to live in the presence of the drug. When TB becomes resistant to INH, INH does not work as well at fighting the bacteria. This study will treat people with INH-resistant TB with different doses of INH to see if INH can still fight the bacteria if we just increase the dose. We will compare how well the drug works at higher doses for participants who have resistant TB to how well the drug works at regular doses for participants who have TB that is not resistant. The study will also compare the safety and tolerability of the different doses of INH. Tolerability is how well people can put up with the side effects of a drug. Using increased doses of INH to treat TB that is resistant to INH is experimental and has not been approved by regulatory authorities. While there is some evidence that this approach will work, this has not yet been proven.

This study will be done in two stages. Stage 1 is a pilot study. A pilot study is a small study that is done before a larger study, to help determine if a larger study will be possible. This pilot study is a small study that will help us determine if it will be possible to enroll enough participants into Stage 2, which is the larger stage of this study. You will be enrolled in Stage 1. If Stage 1 is successful, then Stage 2 will begin.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

After you have signed this consent form, you will have a screening visit. For this screening visit, your study doctor may decide you need to be admitted to the hospital. If you have stopped taking INH recently, you may need to be admitted to the hospital for up to 7 days before screening so that there is time for the INH to wash out of your body. During the screening, you will be asked to provide sputum (cough up phlegm). That sputum will be checked for the bacteria that cause TB. If they are found, your sputum will be tested to see if the TB bacteria in your body are resistant to INH and if it is low-level or high-level resistance. (With low-level resistance, the bacteria are not as resistant to INH as they are with high-level resistance.) Depending on the result of this test, you will be assigned to a group as follows:

- Group 1: Low Level INH Resistance

  If you have low-level INH resistance but you do not meet all eligibility criteria, and you are one of the first 16 to 70 participants in this group, you will be enrolled in the study for one day only and you will be asked to provide a sputum sample. The sample you provide will help us see how much INH is needed to prevent your TB from growing in a test tube. After you provide this sputum sample, you will be finished with the study. You will not receive INH treatment. Instead, you will be referred to receive standard TB treatment outside the study. (See Attachment A, Study Schedule for Participants Providing a Sputum Sample Only.)

  If you have low-level INH resistance and you meet all eligibility criteria, and you are one of the first 15 participants, you will be enrolled into the study and you will receive study treatment. You will be randomized to receive 5, 10, or 15 mg/kg INH once a day for 7 days. Randomized means that you have an equal chance of being assigned to any of the three doses. (Mg/kg, or milligrams per kilogram, means the amount of INH in milligrams you will receive for each kilogram you weigh). INH will be provided for you. In addition, you must take vitamin B_6 once a day while taking INH, to help prevent possible side effects of INH. Vitamin B_6 will also be provided to you. You may need to take up to 13 tablets of INH and an additional tablet of vitamin B_6 daily. While you are receiving study treatment, you will be hospitalized. Attachment A, Study Schedule for Participants Receiving Study Treatment, explains what evaluations you will have.

  You will be referred to appropriate treatment for your TB after you complete study treatment, no later than Day 10 of the study.

- Group 2: No INH Resistance

  If you have no INH resistance and you are one of the first 48 to 64 participants in this group, you will be enrolled in the study for one day only and you will be asked to provide a sputum sample. The sample you provide will help us see how much INH is needed to prevent your TB from growing in a test tube. After you provide this sputum sample, you will be finished with the study. You will not receive INH treatment. Instead, you will be referred to receive standard TB treatment outside the study. (See Attachment A, Study Schedule for Participants Providing a Sputum Sample Only.)

- Group 3: High-level INH Resistance

  If you have high-level INH resistance, and you are one of the first 64 participants in this group, you will be enrolled in the study for one day only and you will be asked to provide a sputum sample. The sample you provide will help us see how resistant your TB infection is to INH. After you provide this sputum sample, you will be finished with the study. You will not receive INH treatment. Instead, you will be referred to receive standard TB treatment outside the study. (See Attachment A, Study Schedule for Participants Providing a Sputum Sample Only.)

If you do not enroll into the study
If you decide not to take part in this study or if you do not meet the eligibility requirements, you will be referred without delay to appropriate treatment for your TB. We will still use some of your information. As part of this screening visit, some demographic (e.g., age, gender, race), clinical (e.g., disease condition, diagnosis), and laboratory information is being collected from you so that researchers may help determine whether there are patterns or common reasons why people do not join a study.

What if I have to permanently stop taking study-provided INH after I start taking it?
During the study:

If you must permanently stop taking study-provided INH, you will be taken off the study. The study staff will discuss other options that may be available to you.

After the study:

After you have completed your study participation, the study will not continue to provide you with INH you received on the study. You will be referred for full TB treatment which always requires more than one drug and may or may not include INH.

Other
If you agree, some of your blood that is left over after all required study testing is done may be stored (with usual protections of your identity) and used for future ACTG-approved research that is separate from this study. Genetic testing will not be done on these blood samples. Samples collected from you will be stored in a laboratory called the Biomedical Research Institute in Rockville, Maryland, United States. These samples may be stored for an unknown period of time. Results of testing performed on these samples will not be given to you. You may withdraw your consent for research on stored specimens at any time, and the specimens will be discarded. No matter what you decide, it will not affect your participation in the study.

_____ YES, I agree to have my leftover blood stored.

_____ NO, I do not agree.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Stage 1 of the study closed to accrual on March 26, 2015. A total of 71 participants provided a sputum sample only, and 15 participants received study treatment.

HOW LONG WILL I BE IN THIS STUDY?

Participants who receive study treatment will be in the study for 20-25 days after enrollment. Participants who will provide a sputum sample only will participate in a single study visit and then be discontinued from the study.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- the study is stopped or cancelled
- you are not able to cough up enough phlegm during the study
- you are unable to complete the hospital stay
- you do not take one or more doses of the study drug
- continuing the study drugs may be harmful to you
- you need a treatment that you may not take while taking the study drugs
- you become pregnant

WHAT ARE THE RISKS OF THE STUDY?

The INH used in this study may have side effects, some of which are listed below. Please note that the list below does not include all the side effects seen with this drug. This list includes the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects, please ask the medical staff at your site.

The INH treatment you receive in this study is not the standard TB treatment. Treatment with just INH may have little to no effect on the bacteria that are causing your TB, depending on how resistant these bacteria are to INH. After you leave the study, you will be referred for TB treatment that will include a full course of effective TB treatment, which will include more than one anti-TB drug. It is very important that you complete this full TB treatment as prescribed. If you do not complete treatment, the bacteria in your body could become resistant to anti-TB drugs.

<u>Risks of Antibacterial Drugs</u>
Some medications used to treat TB may be associated with diarrhea/loose or watery bowels) including bloody diarrhea, which may be serious.

Isoniazid (INH)
The following side effects have been associated with the use of INH:

Serious and sometimes life-threatening liver damage may develop even after many months of treatment. Older age, already having some liver disease, drinking alcohol regularly, and using injection drugs are all associated with an increased risk of developing liver damage. Women, particularly black and Hispanic women, or if they are pregnant or recently gave birth to a baby, may also be at increased risk of life-threatening liver damage. If you develop any of the following symptoms, you should call your doctor right away:

- unexplained loss of appetite
- nausea and/or vomiting
- pale colored stools
- yellowing of the eyes or skin
- pain in the upper abdomen
- dark urine

Additional side effects may include:

- tingling and numbness in the hands and feet
- memory loss, confusion, trouble sleeping, changes in behavior or mood
- unsteadiness or dizziness
- seizures
- low blood counts
- rash and itching
- high blood sugar
- joint pain
- reduced vitamin B_6 levels (a vitamin that helps with many functions in your body)

Non-Study Medications
There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drug. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. In addition, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Risks of Drawing Blood and Having an Indwelling Catheter
Taking blood may cause some discomfort, bleeding, bruising, and/or swelling where the needle enters the body, lightheadedness, and in rare cases, fainting or infection. There is a very small risk of infection or a blood clot from the indwelling catheter.

Risks of Chest X-ray
The amount of high-energy radiation used in a chest x-ray is relatively small and does not pose any significant risk to you.

Risk of Hospitalization
While you are in the hospital, you may be exposed to other patients who have TB that is more resistant to drug treatment (multidrug-resistant TB [MDR-TB] or extensively drug-resistant TB [XDR-TB]). You will be separated from these patients; they will be hospitalized on a different ward and safety precautions will be taken to prevent transmission of disease. Patients who have been treated for MDR-TB or who have been exposed to XDR-TB will not be included in this study.

Risks of Social Harm
It is possible that participating in this study will make it difficult for you to keep your TB status secret from people close to you. If you are infected with HIV, the virus that causes AIDS, it may also be difficult to keep this secret from people close to you. This may lead to unwelcome discussions about or reactions to your HIV or TB status. Please talk with the study staff if you have any concerns about this.

ARE THERE RISKS RELATED TO PREGNANCY?

INH may be unsafe for unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant while you are participating in this study. You must use one of the following barrier methods of birth control that you discuss with the study staff:

- male or female condoms
- intrauterine device (IUD)
- *diaphragm or cervical cap [Remove if not approved by your country's national regulatory authority.]*

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you are in the study and you receive study treatment, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help future patients who have TB.

If you are in the study and asked to provide a sputum sample only, there is no direct benefit to you for participating in this study. Collecting your sputum will help us learn about how likely it is that INH will work to treat patients like you in the future.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

The study-provided drug, laboratory tests to monitor how well this drug is working, and quality medical care may or may not be available to you outside the study. The clinic staff will discuss with you other treatment choices in your area and the risks and the benefits of all the choices.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. *[Insert language about any local disclosure requirements for HIV status.]* Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the ACTG, Office for Human Research Protections (OHRP), *your country's national health agency*, *(insert name of site)* institutional review board (IRB)/ethics committee (EC), National Institutes of Health (NIH), **other local, US, and international regulatory entities**, study staff, and study monitors. (An IRB or EC is a committee that watches over the safety and rights of research participants.)

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME?

There will be no cost to you for study-related visits, physical examinations, laboratory tests or other procedures. *Taking part in this study may lead to added costs to you and your medical insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.*

WHAT HAPPENS IF I AM INJURED OR, IF I BECOME PREGNANT, MY BABY IS INJURED?

If you or your baby is injured as a result of your being in this study, you or your baby will be given immediate treatment for injuries and be referred for further treatment, if necessary. *However, you may/may not (per site/country policy) have to pay for this care.* There is no program for compensation either through (*this institution)* or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or you may leave this study at any time. The care that you would normally receive will not be affected if you decide not to take part. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research participant, contact:

- name or title of person on the IRB or EC or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE ACTG Study A5312

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to take part in this study, please sign your name below.

Participant's Name (print)	Participant's Signature and Date
Participant's Legal Representative (print) (As appropriate)	Legal Representative's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
Witness's Name (print) (As appropriate)	Witness's Signature and Date

ATTACHMENT A
A5312 Stage 1 Study Visits

The study staff can answer any questions you have about individual study visits, the evaluations that will occur, or how long each visit will be. The table below can be used as a quick reference for you, along with the explanations that follow.

I. **Appendix I, Table 1:** Study Schedule for Participants Providing a Sputum Sample Only (some Group 1 participants, and all Group 2 and 3 participants)

Evaluation or Procedure	Screening[1]	Entry[2]
Consent & contact information collected	√	
Sputum collected	√	√

[1]Screening: If your doctor thinks it is best, you may be admitted to the hospital during screening.

[2]Entry: If you are enrolled, you will have a sputum sample collected and then be discontinued from the study and referred for standard local TB treatment.

II. Explanation of Evaluations for Participants Providing a Sputum Sample Only

Below are descriptions of the evaluations for participants who do not receive study treatment. You will be told the results of all tests performed.

Consent and contact information collected: After you read the consent and have had a chance to ask questions about the study, you will sign the consent form if you want to continue and join the study. You will also be asked how to be contacted, and whether you give the study team permission to contact you.

Sputum collected: You will be asked to provide sputum samples. To provide this sample, you will be asked to cough deeply and then spit into a cup. If you need help to cough deeply, the clinic staff may ask you to briefly breathe a mist of saltwater through a tube or a mask. This sputum will be checked for the bacteria that causes TB and to see if these bacteria are resistant to INH.

III. **Appendix I, Table 2:** Study Schedule for Participants Receiving Study Treatment (some Group 1 participants)

Evaluation or Procedure	Screening [1]	Pre-entry[2]	Entry[3]	Study Treatment[4]	Discharge [5]	Final Visit[6]	Early Discontinuation[7]
Consent & contact information collected	√						
HIV status	√						
Chest x-ray	√						
Physical exam	√		√	√	√	√	√
Blood collected	√		√	Days 6 and 7 only		√	√
Pregnancy test	√		√				√
Saliva collected			√				
Sputum collected	√	√	√	√			

[1]Screening: After you have read and signed the consent form, you will have a physical exam and several tests done to make sure that you meet the requirements for joining the study. If your doctor thinks it is best, you may be admitted to the hospital during screening.

[2]Pre-entry: If you qualify for the study based on your screening tests, you will be admitted to the hospital, if you were not during screening.

[3]Entry: If you are enrolled, you will remain in the hospital. At this visit, you will receive your treatment assignment.

[4]Study Treatment: You will receive daily INH treatment while in the hospital.

[5]Discharge: On Day 8, you will be released from the hospital

[6]Final Visit: You will come to the clinic for a final visit about 14 days after you are released from the hospital.

[7]Early Discontinuation: If you stop the study early, you will be asked to come in for a final visit.

IV. Explanation of Evaluations for Participants Receiving Study Treatment (some Group 1 participants)

Below are descriptions of the evaluations for participants who receive study treatment. You will be told the results of all tests performed.

Consent and contact information collected: After you read the consent and have had a chance to ask questions about the study, you will sign the consent form if you want to be screened for the study. You will also be asked how to be contacted, and whether you give the study team permission to contact you.

HIV status: If there is no record available, another HIV test will be done. If an HIV test has to be done, you may have to sign a separate consent form before this is done. You will be told the results of the HIV test as soon as it is available. You may experience stress while waiting for the results of the HIV test.

Chest x-ray: You will have a chest x-ray at screening, if you have not had one done within 14 days before screening.

Physical examination: You will have a physical exam and will be asked questions about your health and about any medications you have taken or are taking now.

Blood collected: Blood will be collected from you for various tests during the study. These include routine blood tests for safety. If you have HIV, you will also have a CD4+ count (a test that shows how many infection-fighting cells you have in your blood).

At entry, blood will be collected for a NAT2 genetic test, which looks at changes in a single human gene that may affect how quickly your body breaks down INH. A gene is a small unit in your body that carries instructions for how your body works. This test will not look at any other genes.

At Day 6 during study treatment, blood will be collected to look at the level of INH. Blood will be collected 9 times over a 24-hour period. An indwelling catheter (a small, thin tube) may be put into an arm vein and left in place. This will allow the blood samples to be drawn without any additional needle sticks. If a catheter cannot be placed or kept in your arm vein, the blood draw will be done by putting a needle in your vein and drawing blood 9 different times.

Blood volume by visit is as follows:

Screening visit: 10 mL (about 2 teaspoons)
Pre-entry visit: 10 mL (about 2 teaspoons)
Study treatment, Day 6 visit: 32 mL (about 8 teaspoons)
Study treatment, Day 7 visit: 6 mL (about 1 teaspoon)
Final visit or early discontinuation visit: 6 mL (about 1 teaspoon)

Pregnancy test: If you are a woman who is able to become pregnant, you will be asked to give a small urine or blood sample (about 5 mL or 1 teaspoon) for a pregnancy test.

Saliva collected: Saliva will be collected for the NAT2 genetic test, which looks at changes in a single human gene that may affect how quickly your body breaks down INH. This test will not look at any other genes.

Sputum collected: You will be asked to provide sputum samples. To provide this sample, you will be asked to cough deeply and then spit into a cup. If you need help to cough deeply, the clinic staff may ask you to briefly breathe a mist of saltwater through a tube or a mask. At pre-entry, entry, and days 1 through 7, sputum will be collected each night (starting around 4 PM) for 16 hours. This sputum will be checked for the bacteria that causes TB and to see if these bacteria are resistant to INH.

APPENDIX II: SAMPLE INFORMED CONSENT FOR PROTOCOL A5312, STAGE 2, STEP 1

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)

The Early Bactericidal Activity of High-Dose or Standard-Dose Isoniazid among Adult Participants with Isoniazid-Resistant or Drug-Sensitive Tuberculosis
FINAL Version **3.0, August 21, 2018**

INTRODUCTION

You are being asked to take part in this research study because you have pulmonary tuberculosis (TB), a bacterial infection in your lungs. This research study is conducted by the AIDS Clinical Trials Group (ACTG), which is a research organization based in the United States. Although the name contains the word “AIDS”, this study is not about research on AIDS or HIV. This study is sponsored by the United States National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Isoniazid (INH) is a drug commonly used to treat TB worldwide. Sometimes, the bacteria that cause TB can become resistant to INH. Resistance means that bacteria have adapted to a drug and are able to live in the presence of the drug. When TB becomes resistant to INH, INH does not work as well at fighting the bacteria. This study will treat people with INH-resistant TB with different doses of INH to see if INH can still fight the bacteria if we just increase the dose. We will compare how well the drug works at higher doses for participants who have resistant TB to how well the drug works at regular doses for participants who have TB that is not resistant. The study will also compare the safety and tolerability of the different doses of INH. Tolerability is how well people can put up with the side effects of a drug. Using increased doses of INH to treat TB that is resistant to INH is experimental and has not been approved by regulatory authorities. While there is some evidence that this approach will work, this has not yet been proven.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

After you have signed this consent form, you will have a screening visit. During the screening, you will be asked to provide sputum (cough up phlegm). That sputum will be checked for the bacteria that cause TB. If they are found, your sputum will be tested to see if the TB bacteria in your body are resistant to INH and if it is low-level or high-level resistance. (With low-level

resistance, the bacteria are not as resistant to INH as they are with high-level resistance.) Depending on the result of this test, you will be assigned to a group as follows:

- Group 1: Low-Level INH Resistance

  If you have low-level INH resistance but you do not meet all eligibility criteria, and you are one of the first 16 to 70 participants in this group, you will be enrolled in the study for one day only and you will be asked to provide a sputum sample. The sample you provide will help us see how much INH is needed to prevent your TB from growing in a test tube. After you provide this sputum sample, you will be finished with the study. You will not receive INH treatment. Instead, you will be referred to receive standard TB treatment outside the study. (See Attachment A, Study Schedule for Participants Providing a Sputum Sample Only.)

- Group 2: No INH Resistance

  If you have no INH resistance but you do not meet all eligibility criteria and you are one of the first 64 **to 84** participants in this group, you will be enrolled in the study for one day only and you will be asked to provide a sputum sample. The sample you provide will help us see how much INH is needed to prevent your TB from growing in a test tube. After you provide this sputum sample, you will be finished with the study. You will not receive INH treatment. Instead, you will be referred to receive standard TB treatment outside the study. (See Attachment A, Study Schedule for Participants Providing a Sputum Sample Only.)

- Group 3: High-Level INH Resistance

  If you have high-level INH resistance, you will be enrolled in the study for one day only and you will be asked to provide a sputum sample. The sample you provide will help us see how resistant your TB infection is to INH. After you provide this sputum sample, you will be finished with the study. You will not receive INH treatment. Instead, you will be referred to receive standard TB treatment outside the study. (See Attachment A, Study Schedule for Participants Providing a Sputum Sample Only.) There will be 64 **to 84** people enrolled in Group 3.

After you provide a sputum sample, you will be invited to participate in Step 2 of the study. Step 2 is the TB treatment part of the study. For this, you will have another screening visit and if you meet all the eligibility criteria, you will be admitted to hospital and receive study medication.

<u>If you do not enroll into the study</u>
If you decide not to take part in this study or if you do not meet the eligibility requirements, you will be referred without delay to appropriate treatment for your TB. We will still use some of your information. As part of this screening visit, some demographic (e.g., age, gender, race), clinical (e.g., disease condition, diagnosis), and laboratory information is being collected from you so that researchers may help determine whether there are patterns or common reasons why people do not join a study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to **218** participants will provide a sputum sample only.

HOW LONG WILL I BE IN THIS STUDY?

Participants who will provide a sputum sample only will participate in a single study visit and then be discontinued from the study.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- the study is stopped or cancelled
- you are not able to cough up enough phlegm during the study

WHAT ARE THE RISKS OF THE STUDY?

Risks of Social Harm
It is possible that participating in this study will make it difficult for you to keep your TB status secret from people close to you. If you are infected with HIV, the virus that causes AIDS, it may also be difficult to keep this secret from people close to you. This may lead to unwelcome discussions about or reactions to your HIV or TB status. Please talk with the study staff if you have any concerns about this.

ARE THERE RISKS RELATED TO PREGNANCY?

As you are only giving a sputum sample and you are taking no study-provided medicine, there is no risk for unborn babies.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

There is no direct benefit to you for participating in this study. Collecting your sputum will help us learn about how likely it is that INH will work to treat patients like you in the future.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Quality medical care may or may not be available to you outside the study. The clinic staff will discuss with you other choices in your area and the risks and the benefits of all the choices.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. *[Insert language about any local disclosure requirements for HIV status.]* Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the ACTG, Office for Human Research Protections (OHRP), *your country's national health agency*, *(insert name of site)* institutional review board (IRB)/ethics committee (EC), National Institutes of Health (NIH), **other local, US, and international regulatory entities**, study staff, and study monitors. (An IRB or EC is a committee that watches over the safety and rights of research participants.)

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME?

There will be no cost to you for study-related visits, physical examinations, laboratory tests or other procedures. *Taking part in this study may lead to added costs to you and your medical insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.*

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of your being in this study, you will be given immediate treatment for injuries and be referred for further treatment, if necessary. *However, you may/may not (per site/country policy) have to pay for this care.* There is no program for compensation either through (*this institution)* or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or you may leave this study at any time. The care that you would normally receive will not be affected if you decide not to take part. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research participant, contact:

- name or title of person on the IRB or EC or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE ACTG Study A5312

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to take part in this study, please sign your name below.

Participant's Name (print)	Participant's Signature and Date
Participant's Legal Representative (print) (As appropriate)	Legal Representative's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
Witness's Name (print) (As appropriate)	Witness's Signature and Date

ATTACHMENT A
A5312 Stage 2, Step 1 Study Visits

The study staff can answer any questions you have about individual study visits, the evaluations that will occur, or how long each visit will be. The table below can be used as a quick reference for you, along with the explanations that follow.

I. **Appendix II Table 1:** Study Schedule for Participants Providing a Sputum Sample Only (some Group 1**, 2, and 3** participants)

Evaluation or Procedure	Screening[1]	Entry[2]
Consent & contact information collected	√	
Sputum collected	√	√

[1]Screening: If your doctor thinks it is best, you may be admitted to the hospital during screening.

[2]Entry: If you are enrolled, you will have a sputum sample collected and then be discontinued from the study and referred for standard local TB treatment.

II. Explanation of Evaluations for Participants Providing a Sputum Sample Only

Below are descriptions of the evaluations for participants who do not receive study treatment. You will be told the results of all tests performed.

Consent and contact information collected: After you read the consent and have had a chance to ask questions about the study, you will sign the consent form if you want to continue and join the study. You will also be asked how to be contacted, and whether you give the study team permission to contact you.

Sputum collected: You will be asked to provide **a** sputum sample. To provide this sample, you will be asked to cough deeply and then spit into a cup. If you need help to cough deeply, the clinic staff may ask you to briefly breathe a mist of saltwater through a tube or a mask. This sputum will be checked for the bacteria that causes TB and to see if these bacteria are resistant to INH.

APPENDIX III: SAMPLE INFORMED CONSENT FOR A5312: STAGE 2, STEP 2

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INTRODUCTION

You are being asked to take part in this research study because you have pulmonary tuberculosis (TB), a bacterial infection in your lungs. You participated in the Stage 2, Step 1 part of this study. You have given a sputum sample which has been tested, and the bacteria causing TB has been found in your sputum. The TB bacteria in your body are either not resistant to **INH, have** a low level of INH resistance (the TB bacteria are not that resistant to INH)**, or have a high level of INH resistance (the TB bacteria are more resistant to INH).** This is why you have been asked to take part in Step 2 of the study.

This research study is conducted by the AIDS Clinical Trials Group (ACTG), which is a research organization based in the United States. Although the name contains the word “AIDS”, this study is not about research on AIDS or HIV. This study is sponsored by the United States National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Isoniazid (INH) is a drug commonly used to treat TB worldwide. Sometimes, the bacteria that cause TB can become resistant to INH. Resistance means that bacteria have adapted to a drug and are able to live in the presence of the drug. When TB becomes resistant to INH, INH does not work as well at fighting the bacteria. This study will treat people with INH-resistant TB with different doses of INH to see if INH can still fight the bacteria if we just increase the dose. We will compare how well the drug works at higher doses for participants who have resistant TB to how well the drug works at regular doses for participants who have TB that is not resistant. The study will also compare the safety and tolerability of the different doses of INH. Tolerability is how well people can put up with the side effects of a drug. Using increased doses of INH to treat TB that is resistant to INH is experimental and has not been approved by regulatory authorities. While there is some evidence that this approach will work, this has not yet been proven.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

After you have signed this consent form, you will have a screening visit. For this screening visit, your study doctor may decide you need to be admitted to the hospital. If you have stopped taking INH recently, you may need to be admitted to the hospital for up to 7 days before screening so that there is time for the INH to wash out of your body. During Stage 2, Step 1 screening, you were asked to provide sputum (cough up phlegm). That sputum was checked for the bacteria that cause TB, if the TB bacteria in your body are resistant to INH, and if it is low-level or high-level resistance. (With low-level resistance, the bacteria are not as resistant to INH as they are with high-level resistance.) Depending on the result of this test, you will be assigned to a group as follows:

- Group 1: Low-Level INH Resistance

  If you have low-level INH resistance and you meet all eligibility criteria, you will be enrolled into the study and you will receive study treatment. You will be randomized to receive 5, 10, or 15 mg/kg INH once a day for 7 days. Randomized means that you have an equal chance of being assigned to any of the three doses. (Mg/kg, or milligrams per kilogram, means the amount of INH in milligrams you will receive for each kilogram you weigh). Attachment A, Study Schedule for Participants Receiving Study Treatment, explains what evaluations you will have.

- Group 2: No INH Resistance

  If you have no INH resistance and you meet all eligibility criteria, **you will be enrolled into the study and you will receive study treatment of 5 mg/kg INH once a day for 7 days.** Attachment A, Study Schedule for Participants Receiving Study Treatment, explains what evaluations you will have.

- **Group 3: High-Level INH Resistance**

  If you have high-level INH resistance and you meet all eligibility criteria, you will be enrolled into the study and you will receive study treatment of 15 or 20 mg/kg INH once a day for 7 days. Attachment A, Study Schedule for Participants Receiving Study Treatment, explains what evaluations you will have.

INH will be provided for you. In addition, you must also take vitamin B_6 once a day while taking INH, to help prevent possible side effects of INH. Vitamin B_6 will also be provided to you. You may need to take up to 13 tablets of INH and an additional tablet of vitamin B_6 daily. While you are receiving study treatment, you will be hospitalized.

You will be referred to appropriate treatment for your TB after you complete study treatment, no later than Day 10 of the study.

<u>If you do not enroll into the study</u>
If you decide not to take part in this study or if you do not meet the eligibility requirements, you will be referred without delay to appropriate treatment for your TB. We will still use some of your

information. As part of this screening visit, some demographic (e.g., age, gender, race), clinical (e.g., disease condition, diagnosis), and laboratory information is being collected from you so that researchers may help determine whether there are patterns or common reasons why people do not join a study.

What if I have to permanently stop taking study-provided INH after I start taking it?

During the study:

If you must permanently stop taking study-provided INH, you will be taken off the study. The study staff will discuss other options that may be available to you.

After the study:

After you have completed your study participation, the study will not continue to provide you with INH you received on the study. You will be referred for full TB treatment which always requires more than one drug and may or may not include INH.

Other

If you agree, some of your blood that is left over after all required study testing is done may be stored (with usual protections of your identity) and used for future ACTG-approved research that is separate from this study. Genetic testing will not be done on these blood samples. Samples collected from you will be stored in a laboratory called the Biomedical Research Institute in Rockville, Maryland, United States. These samples may be stored for an unknown period of time. Results of testing performed on these samples will not be given to you. You may withdraw your consent for research on stored specimens at any time, and the specimens will be discarded. No matter what you decide, it will not affect your participation in the study.

_____ YES, I agree to have my leftover blood stored.

_____ NO, I do not agree.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Between 64 and 84 participants will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

Participants will be in the study for 20-25 days after enrollment.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- the study is stopped or cancelled
- you are not able to cough up enough phlegm during the study
- you are unable to complete the hospital stay
- you do not take one or more doses of the study drug
- continuing the study drugs may be harmful to you
- you need a treatment that you may not take while taking the study drugs
- you become pregnant

WHAT ARE THE RISKS OF THE STUDY?

The INH used in this study may have side effects, some of which are listed below. Please note that the list below does not include all the side effects seen with this drug. This list includes the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects, please ask the medical staff at your site.

The INH treatment you receive in this study is not the standard TB treatment. Treatment with just INH may have little to no effect on the bacteria that are causing your TB, depending on how resistant these bacteria are to INH. After you leave the study, you will be referred for TB treatment that will include a full course of effective TB treatment, which will include more than one anti-TB drug. It is very important that you complete this full TB treatment as prescribed. If you do not complete treatment, the bacteria in your body could become resistant to anti-TB drugs.

Risks of Antibacterials
Some medications used to treat TB may be associated with diarrhea/loose or watery bowels) including bloody diarrhea, which may be serious.

Isoniazid (INH)
The following side effects have been associated with the use of INH:

Serious and sometimes life-threatening liver damage may develop even after many months of treatment. Older age, already having some liver disease, drinking alcohol regularly, and using injection drugs are all associated with an increased risk of developing liver damage. Women, particularly black and Hispanic women, or if they are pregnant or recently gave birth to a baby, may also be at increased risk of life-threatening liver damage. If you develop any of the following symptoms, you should call your doctor right away:

- unexplained loss of appetite
- nausea and/or vomiting
- pale colored stools
- yellowing of the eyes or skin

- pain in the upper abdomen
- dark urine

Additional side effects may include:

- tingling and numbness in the hands and feet
  memory loss, confusion, trouble sleeping, changes in behavior or mood
- unsteadiness or dizziness
- seizures
- low blood counts
- rash and itching
- high blood sugar
- joint pain
- reduced vitamin B_6 levels (a vitamin that helps with many functions in your body)

The available data from research studies that gave high doses of INH (15–20 mg/kg, as in Group 3) show that high doses of INH are usually well tolerated. More participants in these studies had numbness and tingling in their hands and feet when they took higher doses. Malnourished participants who took higher doses had a higher occurrence of numbness and tingling. Usually, this occurred when high doses of INH were taken for much longer than 7 days. Up to now, in this study (A5312) there have been no serious side effects from the treatment, and there have been no reported episodes of numbness or tingling. To ensure your safety, you will be given vitamin B6 to take once a day; this should help decrease the occurrence of numbness and tingling.

Non-Study Medications

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drug. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. In addition, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Risks of Drawing Blood and Having an Indwelling Catheter

Taking blood may cause some discomfort, bleeding, bruising, and/or swelling where the needle enters the body, lightheadedness, and in rare cases, fainting or infection. There is a very small risk of infection or a blood clot from the indwelling catheter.

Risks of Chest X-ray

The amount of high-energy radiation used in a chest x-ray is relatively small and does not pose any significant risk to you.

Risk of Hospitalization

While you are in the hospital, you may be exposed to other patients who have TB that is more resistant to drug treatment (multidrug-resistant TB [MDR-TB] or extensively drug-resistant TB [XDR-TB]). You will be separated from these patients; they will be hospitalized on a different

ward and safety precautions will be taken to prevent transmission of disease. Patients who have been treated for MDR-TB or who have been exposed to XDR-TB will not be included in this study.

Risks of Social Harm
It is possible that participating in this study will make it difficult for you to keep your TB status secret from people close to you. If you are infected with HIV, the virus that causes AIDS, it may also be difficult to keep this secret from people close to you. This may lead to unwelcome discussions about or reactions to your HIV or TB status. Please talk with the study staff if you have any concerns about this.

ARE THERE RISKS RELATED TO PREGNANCY?

INH may be unsafe for unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant while you are participating in this study. You must use one of the following barrier methods of birth control that you discuss with the study staff:

- male or female condoms
- intrauterine device (IUD)
- *diaphragm or cervical cap [Remove if not approved by your country's national regulatory authority.]*

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you are receiving study treatment and you are in Group 1 **or Group 3**, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help future patients who have TB.

If you are receiving study treatment and you are in Group 2, you have been asked to participate in this study to serve as a control, a group with which the experimental group can be compared to determine how well the experimental treatment is working. There may be no direct benefit to you for participating in this study.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

The study-provided drug, laboratory tests to monitor how well this drug is working, and quality medical care may or may not be available to you outside the study. The clinic staff will discuss with you other treatment choices in your area and the risks and the benefits of all the choices.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. *[Insert language about any local disclosure requirements for HIV status.]* Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the ACTG, Office for Human Research Protections (OHRP), *your country's national health agency*, *(insert name of site)* institutional review board (IRB)/ethics committee (EC), National Institutes of Health (NIH), **other local, US, and international regulatory entities**, study staff, and study monitors. (An IRB or EC is a committee that watches over the safety and rights of research participants.)

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME?

There will be no cost to you for study-related visits, physical examinations, laboratory tests or other procedures. *Taking part in this study may lead to added costs to you and your medical insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.*

WHAT HAPPENS IF I AM INJURED OR, IF I BECOME PREGNANT, MY BABY IS INJURED?

If you or your baby is injured as a result of your being in this study, you or your baby will be given immediate treatment for injuries and be referred for further treatment, if necessary. *However, you may/may not (per site/country policy) have to pay for this care.* There is no program for compensation either through (*this institution)* or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or you may leave this study at any time. The care that you would normally receive will not be affected if you decide not to take part. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research participant, contact:

- name or title of person on the IRB or EC or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE ACTG Study A5312

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to take part in this study, please sign your name below.

Participant's Name (print)	Participant's Signature and Date
Participant's Legal Representative (print) (As appropriate)	Legal Representative's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
Witness's Name (print) (As appropriate)	Witness's Signature and Date

ATTACHMENT A
A5312 Stage 2, Step 2 Study Visits

The study staff can answer any questions you have about individual study visits, the evaluations that will occur, or how long each visit will be. The table below can be used as a quick reference for you, along with the explanations that follow.

I. **Appendix III, Table 1:** Study Schedule for Participants Receiving Study Treatment (some Group 1**, 2, and 3** participants)

Evaluation or Procedure	Screening [1]	Pre-entry[2]	Entry[3]	Study Treatment [4]	Discharge[5]	Final Visit[6]	Early Discontinuation [7]
Consent & contact information collected	√						
HIV status	√						
Chest x-ray	√						
Physical exam	√		√	√	√	√	√
Blood collected	√		√	Days 6 and 7 only		√	√
Pregnancy test	√		√				√
Saliva collected			√				
Sputum collected	√	√	√	√			

[1]Screening: After you have read and signed the consent form, you will have a physical exam and several tests done to make sure that you meet the requirements for joining the study. If your doctor thinks it is best, you may be admitted to the hospital during screening.
[2]Pre-entry: If you qualify for the study based on your screening tests, you will be admitted to the hospital, if you were not during screening.
[3]Entry: If you are enrolled, you will remain in the hospital. At this visit, you will receive your treatment assignment.
[4]Study Treatment: You will receive daily INH treatment while in the hospital.
[5]Discharge: On Day 8, you will be released from the hospital
[6]Final Visit: You will come to the clinic for a final visit about 14 days after you are released from the hospital.
[7]Early Discontinuation: If you stop the study early, you will be asked to come in for a final visit.

II. Explanation of Evaluations for Participants Receiving Study Treatment (some Group 1**, 2, and 3** participants)

Below are descriptions of the evaluations for participants who receive study treatment. You will be told the results of all tests performed.

Consent and contact information collected: After you read the consent and have had a chance to ask questions about the study, you will sign the consent form if you want to be screened for the study. You will also be asked how to be contacted, and whether you give the study team permission to contact you.

HIV status: If there is no record available, another HIV test will be done. If an HIV test has to be done, you may have to sign a separate consent form before this is done. You will be told the results of the HIV test as soon as it is available. You may experience stress while waiting for the results of the HIV test.

Chest x-ray: You will have a chest x-ray at screening, if you have not had one done within 14 days before screening.

Physical examination: You will have a physical exam and will be asked questions about your health and about any medications you have taken or are taking now.

Blood collected: Blood will be collected from you for various tests during the study. These include routine blood tests for safety. If you have HIV, you will also have a CD4+ count (a test that shows how many infection-fighting cells you have in your blood).

At entry, blood will be collected for a NAT2 genetic test, which looks at changes in a single human gene that may affect how quickly your body breaks down INH. A gene is a small unit in your body that carries instructions for how your body works. This test will not look at any other genes.

At Day 6 during study treatment, blood will be collected to look at the level of INH. Blood will be collected 9 times over a 24-hour period. An indwelling catheter (a small, thin tube) may be put into an arm vein and left in place. This will allow the blood samples to be drawn without any additional needle sticks. If a catheter cannot be placed or kept in your arm vein, the blood draw will be done by putting a needle in your vein and drawing blood 9 different times.

Blood volume by visit is as follows:

Screening visit: 10 mL (about 2 teaspoons)
Pre-entry visit: 10 mL (about 2 teaspoons)
Study treatment, Day 6 visit: 32 mL (about 8 teaspoons)
Study treatment, Day 7 visit: 6 mL (about 1 teaspoon)
Final visit or early discontinuation visit: 6 mL (about 1 teaspoon)

Pregnancy test: If you are a woman who is able to become pregnant, you will be asked to give a small urine or blood sample (about 5 mL or 1 teaspoon) for a pregnancy test.

Saliva collected: Saliva will be collected for the NAT2 genetic test, which looks at changes in a single human gene that may affect how quickly your body breaks down INH. This test will not look at any other genes.

Sputum collected: You will be asked to provide sputum samples. To provide this sample, you will be asked to cough deeply and then spit into a cup. If you need help to cough deeply, the clinic staff may ask you to briefly breathe a mist of saltwater through a tube or a mask. At pre-entry, entry, and days 1 through 7, sputum will be collected each night (starting around 4 PM) for 16 hours. This sputum will be checked for the bacteria that causes TB and to see if these bacteria are resistant to INH.