Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. N Engl J Med 2018;379:440-53. DOI: 10.1056/NEJMoa1714283

Supplementary Appendix

TABLE OF CONTENTS:

Parts 1-4 are related to the manuscript: "Four months rifampin versus nine months isoniazid for latent TB in adults". Parts 1-3 also pertain to the manuscript "Safety and tolerability of 4 months rifampin or 9 months isoniazid in children"

PART 1: DETAILS OF ELIGIBILITY CRITERIA (*see also protocol in Supplement Protocols & Statistical Analysis Plan available at NEJM.org*)

Eligibility criteria (from protocol version 6)

Inclusion criteria Adult:

Adults (age > 18) with documented positive TST as defined below and prescribed 9INH for LTBI, by provider, but also considered at increased risk for reactivation - following authoritative recommendations (ATS and Canadian TB Standards):

Note: In the absence of a TST, a positive QFT or T-Spot (according to manufacturer's recommendations - see screening, recruitment and randomization procedures) is equivalent to a TST of 10+ mm.

1. HIV positive, **or** to start TNFa inhibitors, **or** on transplant anti-rejection medications (TST ≥5 mm or QFT +)
2. Close contact: >4 hours contact per week, for > 1 week with person with confirmed active pulmonary TB. (TST ≥5 mm or QFT +). "Active TB" is defined as (1) confirmed smear positive, or (2) smear negative or unknown but culture positive for *M Tuberculosis*. This DOES NOT include someone who is smear and culture negative but being treated anyway.
3. Apical/upper lobe fibronodular disease with area >2cm2 (shown in RCT Quick Guide) (TST ≥5 mm or QFT +)
4. Documented tuberculin conversion within two years. (Increase ≥ 6 mm, with subsequent TST ≥10 mm or QFT +)
5. Diabetes, renal failure, or immuno-compromised from medical condition or therapy (TST ≥10 mm or QFT +)
6. Casual contact: contact of <4 hours/week, with a person with smear positive pulmonary TB. (TST ≥10 mm, QFT +)
7. Tuberculin conversion within 2-5 years. (Increase of 10 mm or more with subsequent TST ≥10 mm or QFT +)
8. Have TWO of the following four factors if TST = 10-14mm or QFT + OR ONE factor if TST >15mm:

8a. Arrival in Canada, Australia, or Saudi Arabia in the past 2 years from countries with WHO estimated incidence greater than 100 per 100,000 (these are listed in the RCT Procedure guide - Appendix 5)

8b. BMI <19 (BMI calculations, see RCT Procedure guide);

8c. Any abnormality on chest x-ray compatible with past-TB infection e.g. calcified granuloma, or hilar lymph nodes, costo-phrenic angle blunting - other than fibronodular disease above.

8d. Cigarette smoking (at least a half pack per day) currently.

In the low and middle-income countries, LTBI therapy will usually be offered only to patients in categories 1& 2, because of resource limitations, resulting in substantial differences in risk of active TB among untreated patients at the different sites. Balanced allocation of risk groups to the two study arms will be maintained by site-stratified randomization.

Inclusion criteria Children:

Children (age <18) with documented positive TST as defined below and prescribed 9INH for LTBI, for the indications below, as currently recommended:

Note: In the absence of a TST test, a positive QFT (or T-Spot) (according to manufacturer's recommendations) (see screening, recruitment and randomization procedures) is equivalent to a TST of 10 mm.

1. HIV positive (TST >5 mm or QFT +).

2. Age 5 or less (TST >5 mm or QFT +).

3. Other reason for immuno-compromised state - such as therapy for malignancy or post-transplant (TST >5 mm or QFT +).

4. Contact: with adult or adolescent with confirmed active contagious pulmonary TB, as defined above. (TST >5 mm or QFT +)

5. Have **both** of the following factors if TST = 10-14mm or QFT + or **one** factor if TST >15mm :

5a. Arrival in Canada, Australia, or Saudi Arabia in the past 2 years from countries with estimated annual incidence of active TB greater than 100 per 100,000

5b. Body mass index (BMI) less than 10th percentile for their age.

Study Exclusion criteria

Adult:

1. Patients who were contacts of TB cases known to be resistant to INH, RIF, or both (i.e. MDR).

2. Known HIV-infected individuals on anti-retroviral agents whose efficacy would be substantially reduced by Rifampin, unless therapy can safely be changed to agents not affected by Rifampin (listed in RCT quick guide - Appendix 5).

3. Pregnant women - Rifampin and INH are considered safe in pregnancy 138, 167, but therapy is usually deferred until 2-3 months post-partum to avoid fetal risk and the potential for increased hepato-toxicity immediately post partum 168.

4. Patient on any medication with clinically important drug interactions with INH or RIF, which their physician believes would make either arm contra-indicated. An updated list of clinically important drug interactions is in the RCT Quick Guide (Appendix 5). This includes women taking hormonal contraceptives who will not take alternative contraception.

5. History of allergy/hypersensitivity to Isoniazid or to Rifampin, Rifabutin or Rifapentine.

6. Active TB. Patients initially suspected to have active TB can be randomized once this has been excluded.

7. Persons who have already started LTBI therapy.

Children:

Criteria 1 to 6 are the same as for adults. Criteria 7- Prior complete LTBI therapy or if children have taken >1 week and are still taking the treatment. Children will be eligible if they took an incomplete LTBI therapy (less than 80% of recommended total dose) but more than 6 months ago.

Rationale for exclusion criteria

Exclusion criteria 1-6 enhance the safety of participants, while criterion 7 is to avoid unnecessary therapy. We are interested in the real world application of Rifampin, and so will include persons potentially at risk for non-completion or for adverse events. To obtain a realistic estimate of safety and tolerability, no patient will be excluded on the basis of age nor history of TB therapy, liver disease, alcohol use, or other medication use (except as specified above). If the treating physician prescribed LTBI therapy, they must have concluded the benefits of therapy outweighed the risks. Similarly, to obtain a realistic estimate of effectiveness, patients at risk of non-completion (homeless, alcoholic, and drug use) will be included. An additional reason for these inclusion criteria is to enhance comparability with earlier trials - which involved subjects who were older, HIV infected , or had other co-morbidities.

PART 2: DETAILS OF ADVERSE EVENT MANAGEMENT, AND ADJUDICATION

Summary of procedures for AEs:

Reliance on adverse events reporting by providers in an open label trial could lead to bias because all providers were aware of the potential for serious adverse events with INH. Some may have had beliefs (either way) regarding potential adverse events with RIF. Hence, provider evaluations were considered potentially biased. Considerable effort was made during the conduct of the trial to ensure standardized evaluation including lab investigations, and management of patients who experienced a potential adverse event. This is described in the first SOP - for the sites, with details on management including investigation, and grading. The Grading is taken from published sources. The second SOP was for the Coordinating centre – who reviewed and managed all AE reports. This task was delegated to a member of the Coordinating Centre team – a nurse with 15 years experience in TB, and trained in this task. She reviewed all reports for completeness and blinding. If incomplete she asked the sites for more info, and once she felt the report was clear enough she sent the report to the AE panel. In some cases she asked the PI to review for completeness and clarity (the PI remained blinded through-out the study, and for each such AE reviewed).

The third SOP was for the AE panel, who also received the SOP for the sites for Grading. Every effort was made to ensure that the evaluation by the three-member AE panel remained blinded. When all members of the AE panel completed their review, the 'AE nurse' reviewed these for Grading (for hepatic and hematologic events she verified that each panel member assigned the correct Grade, since this was based on lab values). She also verified if there was discordance in attribution which was dichotomized as 'unlikely' vs 'possible/probable'. She also looked for discordance in Grading for all non-hematologic and non-hepatic events. These were dichotomized as Grade1-2 vs Grade 3-4. If there was discordance in all 3 judgements (eg for a GI event one member rated "Grade 2, unlikely', another 'Grade 3, possible', and another 'Grade 2, possible'), the AE panel was advised there was discordance, and all 3 were asked to re-review still independently. Usually, this resolved things. If still discordance then the three panel members were told of the three ratings, and asked to review a third time. If this did not resolve things, then a conference call was to be held to discuss together. This was never needed.

For ethical, as well as pragmatic reasons, we did not mandate that patients had to restart study drug, even if the independent panel judged that these events were unlikely to be related to study drug. The decision to restart remained an individual provider and patient decision. The exception was pregnancy. In the protocol patients who became pregnant while on study drug had to stop the study drug permanently. They could restart after delivery, but only then.

SOP (Standard Operating Procedures) for Adverse Event Management – for Trial Sites

Objective(s)

The objective of this standard operating procedure (SOP) is to define the methods of collection, documentation, investigation and assessment, as well as submission and follow-up, of adverse events that may occur in the course of a clinical research study.

The SOP will ensure:

- these actions are in compliance with the standards of Good Clinical Practice
- the safety and protection of study subjects
- the quality of the data produced by the study

Persons/Areas affected

This SOP concerns the co-investigators (and their respective research teams) involved in conducting research with human subjects for the study entitled - *A randomized clinical trial of 4 months Rifampin vs. 9 months Isoniazid for latent tuberculosis infection – Phase 3 effectiveness*.

Definition(s)

I. Adverse Event (AE):

Any untoward medical occurrence in a research subject administered an intervention and which does not necessarily have a causal relationship with this intervention. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an intervention, whether or not related to the intervention (modified from ICH, E6 1.2)

For this study an event will be considered an adverse event if study medication is stopped by the treating team (or stopped by the study subject and the treating team agrees) due to the event (potential side effect of the study medication).

II. Serious Adverse Event (SAE) (ICH, E6 1.50):

Any adverse event that:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

For this study an adverse event will be considered a serious adverse event if it is graded 3, 4 or 5 (refer to Appendix 1 - Adverse events – Relationship to therapy, evaluation, grading and management).

Procedures

1. Generalities

1.1. Principal Investigator Responsibilities

The Principal Investigator is responsible for:

1.1.1. With respect to any AE, ensuring that appropriate medical treatment is provided to a subject during and after his/her participation in the study (ICH, E6 4.3.2);

1.1.2. Promptly (within 24 hours) reporting to the Institutional Research Board (IRB) any AE that is serious and unexpected, as well as any new information that could adversely affect subjects' safety or the conduct of the study (ICH, E6 3.3.8);

1.1.3. In the case of a death, providing the Coordinating centre and IRB with all additional requested information (autopsy reports, medical reports, etc.) (ICH, E6 4.11.3);

1.1.4. According to the protocol, reporting to the Coordinating centre all AEs as soon as possible (within 24 hours) after the event (ICH, E6 4.11.2);

1.1.5. Immediately reporting to the Coordinating centre all serious AEs (ICH, E6 4.11.1);

1.1.6. Accurately and regularly documenting **all** AEs in the source documents and case report forms (CRFs).

2. Data collection and management of adverse events

2.1 A secondary outcome of this study is to compare the rates of AEs during treatment between subjects randomized to the two study medications.

2.2 Although this study is considered a "pragmatic trial" (a study that ascertains treatment effectiveness under routine program conditions), and follow-up is to be in line with standard practice, and conducted by the initial treating physicians and TB clinic staff, **when an AE occurs the study team must be more directive and ensure appropriate management as outlined in the protocol and appendix 1.**

2.3 The following procedures are specific to the collection of subject information to enable appropriate assessment of potential adverse events. Two case report forms (CRF) have been created for this component of the research study – ADVERSE EVENT INITIAL EVALUATION FORM and ADVERSE EVENT FINAL EVALUATION FORM. The initial form is used to report when an AE has occurred and the final form is used to report how the AE was managed by the treating team.

2.3.1. The ADVERSE EVENT INITIAL EVALUATION FORM CRF must be **promptly** filled out for each study subject when an AE has occurred (see appendix 2 for details on data to be collected).

2.3.2. The information from the CRF must be promptly entered into the study website in order for the initial information about the subject's AE to be transmitted to the Coordinating centre.

2.3.3. Log on to the website (http://tbera.crc.chus.qc.ca) and choose the subject's study ID number (select subject ID) and then press "select subject", and then press "create an event" under "Subject's menu – Adverse event initial evaluation". (Note – after 20 minutes of inactivity users will be automatically logged off of the website.) If unable to log on to the site, the Coordinating centre should be notified of the event by email and the event information should be entered into the website as soon as possible.

2.3.4. Enter the appropriate study subject information from the CRF into the website and at the end of each section click on the "save as draft" button at the bottom of the screen. The data will be saved and can be modified. Record the event number on the CRF for future reference.

2.3.5. At any point during data entry you may exit this section by pressing the "back" key. It is advisable to always press the "save as draft" key prior to this in order to save any data that has been entered. To return to the AE initial information, select the event number and then click on the "adverse event initial evaluation" button.

2.3.6. Once all the initial evaluation information has been entered, press the "save & close" button to transmit the event information to the Coordinating centre. At this point no further modifications can be made to this data. If any further modifications are required this must be done through the Coordinating center, (refer to Maintenance of Study data SOP).

2.3.7. During the management of the adverse event the ADVERSE EVENT FINAL EVALUATION FORM CRF must be filled out for each study subject (see appendix 2 for details on data to be collected).

2.3.8. The information from the CRF must be promptly entered into the study website in order for the final information about the subject's adverse event to be transmitted to the Coordinating centre.

2.3.9. Log on to the website (http://tbera.crc.chus.qc.ca) and choose the subject's study ID number (select subject ID) and then press "select subject", and then choose the subject's study event number and click on the "adverse event final evaluation" button under "Subject's menu – Adverse event final evaluation". (Note – after 20 minutes of inactivity users will be automatically logged off of

the website.) If unable to log on to the site, the Coordinating centre should be notified that the final information is available and the event final information should be entered into the website as soon as possible.

2.3.10. Enter the appropriate study subject information from the CRF into the website and at the end of each section click on the “save as draft” button at the bottom of the screen. The data will be saved and can be modified.

2.3.11. At any point during data entry you may exit this section by pressing the “back” key. It is advisable to always press the “save as draft” key prior to this in order to save any data that has been entered. To return to the AE final information, select the event number and then click on the “adverse event final evaluation” button.

2.3.12. Once all the final evaluation information has been entered, press the “save & close” button to transmit the event information to the Coordinating centre. At this point no further modifications can be made to this data. If any further modifications are required this must be done through the Coordinating center, (refer to Maintenance of Study data SOP).

References

For Grading: The grading of the severity and the relationship to the therapy are assessed based on ATS guidelines for hepato-toxicity (Ref 155 in protocol), or the National Cancer Institute Common Terminology Criteria for Adverse Events v2.0 and v4.02 (at http://ctep.info.nih.gov/reporting/ctc.html) for all others,

Guidance for Industry. Good Clinical Practice: Consolidated Guideline. ICH Topic E6

SOP09EN01_Adverse Event Management_19jun08 - Research Institute of the McGill University Health Centre

SOP15EN01_On-going Communication with the REB_19jun08 - Research Institute of the McGill University Health Centre

RCT LTBI SOP04EN03 Study Subject Follow-up During Treatment – 19Feb10

RCT LTBI SOP06EN03 Study Subject Follow-up Post Treatment – 19Feb10

RCT LTBI SOP08EN02 Management of study data – 19Feb10

APPENDIX A for Sites - ADVERSE EVENTS
RELATIONSHIP TO THERAPY, EVALUATION, GRADING AND MANAGEMENT*

*adapted from ATS guidelines for hepato-toxicity [155], or the National Cancer Institute Common Terminology Criteria for Adverse Events v2.0 & v4.02 (http://ctep.info.nih.gov/reporting/ctc.html)

Note this information is also available through a link on the website in the Adverse Event Initial Evaluation and the Adverse Event Final Evaluation screens.

Adverse event

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure.

Relationship to therapy

Relationship	Description
Unsure	Further information and follow-up is required.
None	Clear alternative explanation. Very unlikely related to study drug.
Unlikely	Improbable, based on lack of temporal relationship and other explanations exist.
Possible	Reasonable temporal relationship although other explanations also exist.
Probable	Reasonable temporal relationship and unlikely to be any other explanation or cause.

General guidelines for grading the severity of an adverse event **

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to the adverse event.

**Not all Grades are appropriate for all adverse events. Therefore, some adverse events are listed with fewer than five options for Grade selection. Grades for Hepatic and hematologic are based on numerical lab values relative to normal values for that lab. See below.

Refer to the tables on the following pages for detailed information on the evaluation, grading and management for specific types of adverse events.

Drug interaction

Symptoms	• Various symptoms related to specific medications involved.
Medical History	• According to specific medications involved & symptoms.
Investigations	• According to specific medications involved & symptoms. Important to measure drug levels or assess drug effects.
Grading severity	• Grade 1: Potential drug interaction noted but no change in therapy required and neither short- nor long-term effects detected. • Grade 2: Potential drug interaction is noted and after an initial change in therapy no further problems. Subject does not suffer any untoward clinical effect. OR Drug interaction is noted and therapy has to be modified repeatedly but eventually is successful. Subject does not suffer any untoward clinical effect. • Grade 3: Drug interaction noted. Care providers unable to adjust therapy successfully to achieve therapeutic effects. No other adverse effect. • Grade 4: Drug interaction causes serious health problems such as diabetes or hypertensive, or cardiac crisis or results in seizures.
Management	• Grade 1-2: Continue monitoring. • Grade 3 or 4: LTBI therapy must be discontinued.

Gastrointestinal intolerance

Symptoms	• Nausea, Upset stomach, Vomiting • Loss of appetite • Abdominal pain • Diarrhea
Medical History	Subject must be questioned regarding • Alcohol • Past history of other gastrointestinal (GI) problems particularly peptic ulcer or gallbladder disease. GI intolerance must be distinguished from other GI problems including gallbladder (cholecystitis), appendicitis, peptic ulcer, etc. • Use of other potentially causative medications. • Females of childbearing age should be questioned carefully to rule out pregnancy. Physical examination required • Vital signs: temperature, heart rate and blood pressure. • Abdominal exam for signs of peritoneal irritation, tenderness, or mass.
Investigations	• Liver function test (bilirubin, ALT, AST) • Amylase • CBC • Pregnancy test (women of childbearing age) • Abdominal/ Liver ultrasound or X-rays may be performed at discretion of treating team.
Grading severity	• Grade 1: Some upset stomach with nausea and/or loss of appetite but no vomiting and no change in bowel habits. • Grade 2: Nausea with some vomiting, or abdominal pain that is severe enough to disturb daily routine, or persistent diarrhea. • Grade 3: Prolonged nausea and vomiting and/or severe abdominal pain that disrupts daily life (e.g. cannot sleep) severe diarrhea (5 or more BM's/day).

Management	• Grade 1: Change the hours of treatment. Therapy can be taken with meals. • Grade 2: Gravol or other anti-emetic may be given. Try changing the hours of treatment and taking the pills with meals. Take one or two days off all therapy and then try again. A lower dose for the first two to three days may be tried (then resume normal dose). (If this strategy is used, then subject therapy must be prolonged by the total number of days with no or reduced therapy. This interruption is not counted in the calculation of subject compliance.) • Grade 3: Gravol or other anti-emetic may be given. If unsuccessful, stop medication.

Hematologic

Symptoms	• Usually no symptoms, picked up by measuring hematologic parameters.
Medical History	• As necessary, question regarding other medications and diet (particularly if iron deficiency is possible). For females of childbearing age, question regarding menstrual period (heaviness, frequency). • Also question regarding alcohol and use of other possible hematologic suppressants.
Investigations	• B12, folate and iron studies • CBC & differential • Other investigations may be needed
Grading severity	• Grade 1: Neutrophils ≥ 1500/mm3 and < lower limit of normal (LLN) or ≥ 1.5 x 10e9 /L and < LLN OR Platelets ≥ 75,000/mm3 and < LLN or ≥ 75.0 x 10e9 /L and < LLN. • Grade 2: Neutrophils ≥ 1000 and < 1500/mm3 or ≥ 1.0 and <1.5 x 10e9 /L OR Platelets ≥ 50,000 and < 75,000/mm3 or ≥ 50.0 and < 75.0 x 10e9 /L. • Grade 3: Neutrophils ≥ 500 and <1000/mm3 or ≥ 0.5 and <1.0 x 10e9 /L OR Platelets <50,000 and ≥ 25,000/mm3 or < 50.0 and ≥ 25.0 x 10e9 /L. • Grade 4: Neutrophils <500/mm3 or <0.5 x 10e9 /L OR Platelets < 25,000/mm3 or < 25.0 x 10e9/L.
Management	• Grade 1-2: Continue monitoring. • Grade 3 or 4: Review with treating team, evaluate other causes. If no other cause is found and not corrected with B12, folate or iron, discontinue therapy.

Hepatotoxicity

Symptoms	• Anorexia, loss of appetite • Fatigue • Nausea and vomiting • Right upper quadrant pain • Jaundice, dark urine, pale stools • Itching • May have easy bruising, leg edema or abdominal swelling
Medical History	<u>Study subject must be questioned regarding</u> • Alcohol • Use of recreational drugs, prescription, non-prescription drugs & herbal remedies • Past history of liver disease • Injection drug use, transfusions and other risk factors for liver disease <u>Physical examination</u> • Assess the presence of jaundice. • Examine liver for tenderness, enlargement and signs of liver failure (bruising, bleeding, edema and ascites).
Investigations	• Liver function test (bilirubin, ALT, AST) • CBC, INR • HIV, Hepatitis A, B and C serology (unless known positive) • Abdominal / Liver ultrasound may be performed at discretion of treating tea,
Grading severity	• <u>Grade 1-2</u>: ALT/AST 1 to ≤ 3 times upper limit of normal (ULN) plus symptoms as above **OR** ALT/AST 1 to ≤ 5 times ULN and no symptoms. • <u>Grade 3</u>: ALT/ AST 3 to ≤ 10 times ULN plus symptoms as above **OR** ALT/AST 5 to ≤ 10 ULN and no symptoms. • <u>Grade 4</u>: ALT or AST > 10 times ULN.
Management	• <u>Grade 1-2</u>: Therapy should be continued, LFT's should be repeated in 2 weeks. • <u>Grade 3 or 4</u>: Therapy should be discontinued permanently unless there is another explanation for the hepatotoxicity. Follow-up should include ALT and AST approximately weekly until the values return to normal (at least 3 LFT's).

Pregnancy

Symptoms	• Nausea, upset stomach, vomiting • Loss of appetite
Medical History	<u>Subject must be questioned regarding</u> • Sexual activity and contraceptive use • Date of last menstrual period
Investigations	• Pregnancy test
Grading severity	• <u>Grade 3:</u> an unintended pregnancy is considered a grade 3 adverse event
Management	• Stop study drug and consider restarting therapy following completion of the pregnancy.

Rash

Symptoms	• Itching, rash or hives • Location – may be generalized or localized - does it affect limbs, trunk, or face? - is it discrete spots or confluent? - what percentage of total body area is affected? • May cause low blood pressure and weakness, dizziness, or fever. • May cause painful mouth ulcers, eye irritation, wheezing/shortness of breath.
Medical History	Subject must be questioned regarding • Use of drugs including non-prescription drugs, herbal remedies and recreational drugs. • The relationship of the rash to timing of the when medication is taken. • Exposure to other potential allergens, especially food. • Past history of allergies and family history of allergies. Physical examination • Location of the rash: face, trunk (back, stomach, or chest), and limbs. • Appearance of the rash: color (red, purplish, etc.), markings (small spots or large patches), palpable, hives or purpura? • Vital signs: blood pressure and heart rate, and temperature. • Mucus membranes and respiratory system must be examined carefully.
Investigations	• CBC and differential with specific count of eosinophils. • Flow rates (if wheezing is present).
Grading severity	• Grade 1: Itching only, or rash is limited to limbs, or trunk, or face only. Vital signs, mucosal, conjunctiva – all normal. • Grade 2: Rash affects limbs and trunk, or **more than 50%** of total body surface area or is **confluent** in areas. Vital signs mucosa conjunctiva – all normal. • Grade 3: Rash affects 100% of body surface area or mucus membranes, or conjunctiva are affected, or vital signs are abnormal (fever or low blood pressure), or there is wheezing.
Management	• Grade 1: May continue therapy. Give antihistamines. Close follow-up required (daily or every other day). If the rash worsens, management is re-evaluated. • Grade 2: Stop therapy. Give antihistamines. Close follow-up. May re-challenge. • Grade 3: Permanent discontinuation of therapy. Give antihistamines. May need steroids. Follow-up until resolved. Do not re-challenge.

APPENDIX B for sites – ADVERSE INITIAL & FINAL EVALUATION FORMS

The following is a list of explanations for specific fields on the ADVERSE EVENT INITIAL & FINAL EVALUATION FORMS. It does not cover all fields, only those that may require further descriptions or qualifications. For some of the dates, if the study subject is uncertain about the exact date, you can indicate on the form: “exact date is unknown, study subject’s best guess is”.

Research coordinator information – is not entered on web, this data is captured through the user ID.

Why was study medication stopped?
If stopped due to intolerance or if treating team feels they should not stop (the last two options for this question) – do not continue with this form, the subject is now in the follow-up post treatment phase, (refer to SOP06EN02 Study Subject Follow-up Post Treatment)

DESCRIPTION OF ADVERSE EVENT

Most important reason for stopping study medication
Active TB is not an AE it is an outcome and will be investigated separately, (refer to Active TB & Follow-up Post Treatment SOPs)

If pregnancy is the reason for stopping the study medication, the study subject should be contacted approximately every 3 months (using the adverse event final report form to collect information and the adverse event remains open) until after the birth and the study subject restarts treatment or a decision is made not to restart treatment.

Date of resolution of adverse event
This is the date of the clinic visit during which the event is considered “over” and either the study drug is safely restarted, or an alternate management plan is begun.

INITIAL IMPRESSION OR TREATING TEAM
The grading of the severity and the relationship to the therapy are assessed based on
ATS guidelines for hepato-toxicity [155], or the National Cancer Institute Common Terminology Criteria for Adverse Events v2.0 and v4.02 (at http://ctep.info.nih.gov/reporting/ctc.html) for all others,(refer to appendix 1 to for details).

INVESTIGATIONS & TREATMENT PLAN
All investigations in the mandatory column must be performed for the particular type of AE.

For hepatotoxicity – do not need to redo HIV tests if they were done at baseline and it is within 6 months of baseline.

For pregnancy determine number of weeks pregnant and if on birth control at the time of conception. Report this information in the final evaluation **DESCRIPTION**.
Refer to site specific guidelines for whether or not subject is put back on medication following completion of pregnancy.

If subject has study medication restarted successfully, subject returns to follow-up during treatment phase of the study (refer to SOP04EN02 Study Subject Follow-up DuringTreatment).
If subject has study medication restarted successfully, subject returns to follow-up during treatment phase of the study (refer to SOP04EN02 Study Subject Follow-up DuringTreatment).
If study medication is permanently discontinued, subject will then be in the follow-up post treatment phase, (refer to SOP06EN02 Study Subject Follow-up Post Treatment).

Standard Operating Procedures (SOP) for Adverse Event Administration – for Coordinating Centre

Objective

The objective of this standard operating procedure (SOP) is to ensure all adverse events (AE) entered into the website of the study (*A randomized clinical trial of 4 months Rifampin vs. 9 months Isoniazid for latent tuberculosis infection – Phase 3 effectiveness)* are reviewed for completeness and comprehension prior to submitting them to the Adverse Event Independent Panel (AE Panel) members. In addition, this SOP will ensure that all evaluations of AEs performed by the AE panel are reviewed for completeness and comprehension.
The SOP will ensure:

- these actions are in compliance with the standards of Good Clinical Practice
- the safety and protection of study subjects
- the quality of the data produced by the study

Persons/Areas affected

This SOP concerns the members of the study team who are responsible for the administration of the adverse event reporting and evaluations.

Definition(s)

I. **Coordinating centre** – Montreal Chest Institute Site.

Procedures

1. General information

1.1 All AEs must be **promptly** reported (using the initial AE report) to the coordinating centre via the study website. The initial AE report is used as a **notification mechanism** to alert the coordinating centre of the occurrence of an AE, whereas the final AE report must contain all the relevant information about the AE.

1.2 It is the responsibility of the AE Administrator to review all initial AEs to see if there are Deaths (Grade 5), or any potentially serious (Grade 3 or 4) AEs that are unexpected. The PI must be notified of all deaths, and all Grade3-4 AEs that are unexpected, immediately. The AE administrator will also review the final AEs for comprehension and completeness. If an AE is reported in a language other than English, the AE Administrator will contact the coordinating centre for a translation. Translations will be added to the original narratives in the AE reports on the website.

1.3 AE reports with should be prioritized according to their grading severities (priority will be given to those with severities of 3 and greater).

1.4 Once all appropriate information is provided for an AE it must be reviewed by the **blinded** 3 member AE panel.

1.5 Each AE panel member must provide an independent evaluation of each AE within two weeks of notification of an AE.

1.6 All evaluations must be reviewed by the AE administrator.

1.7 A majority is needed (2 out of 3) within the AE panel as to their AE evaluations, specifically for the **Relationship to therapy** (dichotomized into None or Unlikely vs Possible or Probable) and the **Grading severity** (again dichotomized into Grade 1-2 and Grades 3-5) components**.** If the evaluations do not concur, it is the responsibility of the AE Administrator to guide the DSMB members to majority if not to consensus. Refer to point 3.3 below for details.

1.8 For guidance pertaining to the coding of the **Relationship to therapy** or **Grading severity** refer to Appendix 1 below entitled *"Adverse Events: Relationship to Therapy, Evaluation, Grading and Management"* (this document can also be accessed by via a link on the AE screen).

2. Access to Adverse Event Reporting

2.1 Log on to the website (http://tbera.crc.chus.qc.ca) using the Administrative User ID and Password. (Note – after 20 minutes of inactivity users will be automatically logged off of the website.) If unable to log on to the site, contact Karen Hornby (Karen.Hornby@mail.mcgill.ca) at the coordinating centre.

2.2 From the **Administrator management system** screen click on the **Adverse Event Management** box to enter the **Adverse Event Management** screen. This section contains a list of AEs awaiting review, evaluation, or submission of a final report

2.3 The AEs awaiting review are identified with a status of **PENDING** in the **Status Initial** and **Status Final** columns of this list. To access a specific AE, click on **PENDING**. (Note – whenever an AE report has been modified by the study coordinator responsible for the AE, the status will return to **PENDING** and the AE must be reviewed again by the AE Administrator.)

2.4 The initial/final AE report may be read by scrolling through the screen. A template of the information required in an AE report narrative is provided in Appendix 1.

REVIEW OF INITIAL ADVERSE EVENT REPORTS

2.5 Four options are available at the end of the initial report screen:

BACK – Exits the initial AE report screen without submitting any information.

REVIEWED - If feedback should be sent to the user about the AE report, enter it in the "**Write your message below**" box and click on the REVIEWED box. This will update the status of the AE on the list to REVIEWED and an email containing the feedback will be sent to the study coordinator responsible for the AE with a copy to the AE Administrator.

COMPLETED - If no feedback is required, click on the COMPLETED box. This will update the status of the AE on the list to COMPLETED. (Note – the final AE report can not be entered until the initial AE report has been COMPLETED.)

CLOSE NOT AE - If it is determined that the event is not an AE, enter an explanation as to why this is not an AE in the "**Write your message below**" box and click on the CLOSE NOT AE box. This will remove the AE from the list and an email containing the explanation will be sent to the study coordinator responsible for the AE with a copy to the AE Administrator.

2.6 At any point the AE Administrator can modify any of the AE data. (Note – it is preferable to have the site modify the AE data to ensure their adequate understanding of the data). If the data are modified by the AE Administrator the REVIEW option should be used to inform the study coordinator responsible for the AE of the modifications.

REVIEW OF FINAL ADVERSE EVENT REPORTS

2.7 Four options are available at the end of the final report screen:

BACK – Exits the final AE report screen without submitting any information.

REVIEWED - If feedback should be sent to the user about the AE report, enter it in the "**Write your message below**" box and click on the REVIEWED box. This will update the status of the AE on the list to REVIEWED and an email containing the feedback will be sent to the study coordinator responsible for the AE with a copy to the AE Administrator.

COMPLETED - If no feedback is required, click on the COMPLETED box. This will move the AE to each **DSMB member's list of AEs** and to the **Admin list of DSMB evaluations of AEs**. A notification email will

be sent to all DSMB members that an AE is now ready for their review. Once an AE has been sent to the DSMB no modifications can be made to the AE reports.

CLOSE NOT AE - If it is determined that the event is not an AE, enter an explanation as to why this is not an AE in the "**Write your message below**" box and click on the CLOSE NOT AE box. This will remove the AE from the list and an email containing the explanation will be sent to the study coordinator responsible for the AE with a copy to the AE Administrator.

2.8 At any point the AE Administrator can modify any of the AE data. (Note – it is preferable to have the site modify the AE data to ensure their adequate understanding of the data). If the data are modified by the AE Administrator the REVIEW option should be used to inform the study coordinator responsible for the AE of the modifications.

OUTSTANDING FINAL ADVERSE EVENT REPORTS

2.9 If a final AE report has not been entered once an initial report has been COMPLETED, OUTSTANDING will appear in the STATUS FINAL column of the Adverse Event Management screen for the AE.

2.10 If a final AE report has not be entered 1 month after the initial AE report was COMPLETED, DUE will appear in the **Email Reminder** column of the **Adverse Event Management screen** for the AE. A reminder email can be sent to the study coordinator responsible for the AE by clicking on DUE. SENT and the date sent will then appear in the **Email Reminder** column of the **Adverse Event Management screen** for the AE. (Note: DUE will reappear in this column if the final AE report is still not entered after another month.)

3. Access to AE Panel Evaluations of Adverse Events

MANAGEMENT OF AE Panel EVALUATIONS

3.1 Log on to the website (http://tbera.crc.chus.qc.ca) using the Administrative User ID and Password. (Note – after 20 minutes of inactivity users will be automatically logged off of the website.) If unable to log on to the site, contact Karen Hornby (Karen.Hornby@mail.mcgill.ca) at the coordinating centre.

3.2 From the **Administrator management system** screen click on the **AE panel Management** box to enter the **Admin list of Evaluations of AEs** screen. This section contains a list of DSMB evaluations of AEs.

3.3 The evaluations awaiting review are identified with a status of **PENDING** in the **Adverse event evaluation status** columns (one column for each AE Panel member) of this list. The AE Administrator must review all 3 AE Panel member evaluations for each AE. If the evaluations do not concur, it is the responsibility of the AE Administrator to ensure there is at least a majority if not consensus, and to guide the AE Panel members to a majority if not consensus.

General guidelines for evaluating "majority"

(a) **Grading**: should be straight forward as many are based on objective criteria (blood levels). Differences of 1 level are generally acceptable, with the exception of disagreements between grade 2 and 3. This means Grade 1 or 2 are considered to be in agreement, and Grades 3 or 4 are also considered to be in agreement. Death (grade 5) should not have any disagreement. (Grades need to be within the 1 or 2 range OR within the 3 or 4 range)

(b) **Relationship to therapy**: should be fairly close, but do not have to be the same, As with Grading categories are grouped together. No relationship is considered to be in agreement with unlikely, and possible is considered to 'agree' with probable. 'None, unlikely' as a group is much different than 'possible, probable'.

(c) **Consult with Principal Investigator** as required as sometimes this is a judgment call based upon the specifics of the event. Maintain blinding in these discussions with the PI.

To access a specific evaluation, click on **PENDING**.

3.4 The full initial and final AE reports may be read by scrolling through the screen. The **AE Adverse Event** section is at the bottom of the screen. It contains the DSMB evaluation information pertaining to the **Relationship to therapy**, **Grading severity**, and **Type of adverse event** and **Comments** (additional relevant information, or questions from the DSMB member).

3.5 Three options are available at the end of the final report screen:

BACK – Exits the AE evaluation report screen without submitting any information.

REVIEWED - If feedback should be sent to the AE Panel member about the AE evaluation, enter it in the "**Write your message below**" box and click on the REVIEWED box. This will update the status of the AE evaluation on the **Admin list of AE Panel Evaluations of AEs** to REVIEWED and an email containing the feedback will be sent to the AE Panel member with a copy to the AE Administrator. (Note - feedback to AE Panel members must not unblind them to the study medication nor to the evaluations of the other AE Panel members.)

ACCEPT - If no feedback is required, click on the ACCEPT box. This updates the status of the specific DSMB member's evaluation on the **Admin list of AE Panel Evaluations of AEs** screen to COMPLETED. It also moves the evaluation off the specific DSMB member's outstanding list and adds it to their completed list. Once all 3 evaluations are ACCEPTed, they are moved off the **Admin list of AE Panel Evaluations of AEs** screen and on to the **Admin list of completed adverse events/evaluations.** (Note – evaluations should not be ACCEPTed until consensus has been reached between all 3 members of the DSMB).

3.6 The AE Administrator cannot modify any of the AE data nor the AE evaluations at this point. As well the AE Panel members can only modify their respective evaluations and not the contents of the particular AE.

OUTSTANDING EVALUATIONS OF ADVERSE EVENTS

3.7 If an evaluation of an AE report has not been entered once a final report has been COMPLETED, the AE Panel member's column (under the **Adverse event evaluation status** heading of the **Admin list of AE Panel Evaluations of AEs**) will be blank.

3.8 If an evaluation of an AE report has not be entered 2 weeks after the final AE report was COMPLETED, the AE Administrator should send a personalized reminder email to the respective AE Panel member requesting an evaluation be submitted.

COMPLETED ADVERSE EVENT /EVALUATIONS

4.1 To view the list of COMPLETED AEs and their ACCEPTed evaluations, click on **Completed AE/Evaluations** on the **Administrator management system** screen.

4.2 To view a specific AE/Evaluation in the **Admin list of completed adverse events/evaluations**, click on the corresponding COMPLETED "box" under the corresponding AE Panel member's column.

4.3 The full initial and final AE reports as well as the evaluation may be read by scrolling through the screen. The **AE Panel Adverse Event** section is at the bottom of the screen. No further modifications can be made at this point.

4.4 To exit from this screen and return to the **Admin list of completed adverse events/evaluations,** click on the BACK box.

References

Guidance for Industry. Good Clinical Practice: Consolidated Guideline. ICH Topic E6

APPENDIX A – TEMPLATE* FOR ADVERSE EVENT REPORT NARRATIVE

A gender patient, age, smoking/drinking status, comordities, other medication, began study medication on date.
Client states fair/good/excellent compliance.
After time period, client reported/blood results, showed _____ (high AST, nausea etc).

Describe symptoms if any.

Describe what happened after this in sequential order:
When did client come to clinic?
What blood work was done?
Was study medication stopped by client, treating team?
When was study medication stopped?
Provide any subsequent blood work/symptoms.

Describe any actions taken by treating team

General comments
This report should be as concise as possible and NOT include the name of the study medication or any reference which would identify it.
Details regarding history of exposure and TST/PPD status are not necessary.
Ensure that enough information is provided so that the DSMB members are able to determine the relationship to therapy and grading of the AE.

Never include:
Names of anyone
Name of the study medication the study subject was on
Time intervals that will "give away" which study medication the study subject was on – instead use percentages – i.e. study subject had taken 50% of required therapy.
Abbreviations

*For initial AE report provide as much of this information as available at the time of the report. The final AE report should be a comprehensive as possible.

Standard Operating Procedures (SOP) for Evaluations of Adverse Events – for AE Independent Panel

Objective

The objective of this standard operating procedure (SOP) is to ensure appropriate evaluations of adverse events by the Adverse Event Independent Panel (AE Panel) members for the study entitled - *A randomized clinical trial of 4 months Rifampin vs. 9 months Isoniazid for latent tuberculosis infection – Phase 3 effectiveness*.
The SOP will ensure:

- these actions are in compliance with the standards of Good Clinical Practice
- the safety and protection of study subjects
- the quality of the data produced by the study

Persons/Areas affected

This SOP concerns the AE Panel members involved in the study entitled - *A randomized clinical trial of 4 months Rifampin vs. 9 months Isoniazid for latent tuberculosis infection – Phase 3 effectiveness*.

Definition(s)

I. **Coordinating centre** – Montreal Chest Institute Site.

Procedures

1. General information

1.1 All adverse events must be reviewed by the 3 member AE Panel.

1.2 Each AE Panel member must provide an independent evaluation of each adverse event.

1.3 When an adverse event is ready for AE Panel review and evaluation, an automated email is sent to all AE Panel members (from rsrwebmst@Usherbrooke.ca) with the subject heading – "**Adverse event report**" and the contents will be "**An adverse event report has been submitted for subject XXXX and is ready for your evaluation**".

1.4 Adverse event evaluations should be provided by AE Panel members within two weeks of the above noted email notification.

1.5 For guidance pertaining to the coding of the **Relationship to therapy** or the **Grading severity** click on the link "**Click on the link for information on evaluation, grading and management of adverse events**" at the top of the **AE Panel Adverse Event Evaluation** section (see below).

2. Data entry for AE Panel Evaluations of Adverse Events

2.1 Log on to the website (http://tbera.crc.chus.qc.ca) using the User ID and Password previously provided. (Note – after 20 minutes of inactivity users will be automatically logged off of the website.) If unable to log on to the site, contact Karen Hornby (Karen.Hornby@mail.mcgill.ca) at the coordinating centre.

2.2 From the **AE management system** screen click on the **Outstanding AE Evaluations** box to enter the **AE Management** screen. This section contains a list of adverse events awaiting AE Panel review and evaluation.

2.3 The adverse events awaiting an evaluation are identified with a status of **PENDING** in the **Status AE Evaluation** column of this list. To access a specific adverse event, click on **PENDING**.

2.4 The full initial and final adverse event reports may be read by scrolling through the screen. The most informative section is the narrative portion of the final adverse event information (section 6.1 of the **ADVERSE EVENT FINAL EVALUATION FORM**). The initial adverse event section/report is used primarily as a notification of a potential adverse event to the coordinating centre and thus is often incomplete. Once

this has been read, scroll to the **AE Adverse Event** section at the bottom of the screen. Enter the AE evaluation information pertaining to the **Relationship to therapy**, **Grading severity**, and **Type of adverse event** by choosing the appropriate responses from the corresponding drop-down lists. Additional relevant information, or questions if further information is required, may be typed it into the **Comments** box.

2.5 To submit the evaluation, click on the **SAVE & SUBMIT** box at the bottom of the screen. Or to return to the list without submitting any evaluation information click on the **BACK** box.

2.6 To return to the list of adverse events after submitting an evaluation click on **HOME** at the top right corner of the screen**.** Once an evaluation is submitted, the status of the evaluation will be changed to **SUBMITTED** on the **AE Management** screen. At this point the evaluation may be viewed by the AE Panel member by clicking on **SUBMITTED**, however, modifications are no longer permitted.

2.7 Each AE Panel Evaluation will be reviewed by the coordinating centre and if an AE Evaluation requires further review, an email will be sent to the respective AE Panel member with the subject heading "**Query for adverse event evaluation**" and the email will provide information pertaining to the data in question. The status of the particular evaluation will be changed back to **PENDING** on the **AE Management** screen, thus permitting further modifications to the evaluation by the AE Panel member.

2.8 If a Query is received by the AE Panel member, the request outlined in the email should be considered, any appropriate changes to the evaluation should be made and the evaluation should be re-**SUBMITTED** (step 2.2 above).

2.9 Once an evaluation is accepted by the coordinating center, it will automatically be moved from the **AE Management** screen to the **AE Panel list of completed adverse events/evaluations.** To access this information, click on the **Completed AE Evaluations** box on the **AE management system** screen. To view the specific adverse event, click on the date the event was completed in the **Date completed** column.

References

Guidance for Industry. Good Clinical Practice: Consolidated Guideline. ICH Topic E6

APPENDIX for AE Panel - ADVERSE EVENTS RELATIONSHIP TO THERAPY, EVALUATION, GRADING AND MANAGEMENT*

*adapted from ATS guidelines for hepato-toxicity [155], or the National Cancer Institute Common Terminology Criteria for Adverse Events v2.0 & v4.02 (http://ctep.info.nih.gov/reporting/ctc.html)

Note this information is also available through a link on the website in the Adverse Event Initial Evaluation and the Adverse Event Final Evaluation screens.

Adverse event

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure.

Relationship to therapy

Relationship	Description
Unsure	Further information and follow-up is required.
None	Clear alternative explanation. Very unlikely related to study drug.
Unlikely	Improbable, based on lack of temporal relationship and other explanations exist.
Possible	Reasonable temporal relationship although other explanations also exist.
Probable	Reasonable temporal relationship and unlikely to be any other explanation or cause.

General guidelines for grading the severity of an adverse event **

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to the adverse event.

**Not all Grades are appropriate for all adverse events. Therefore, some adverse events are listed with fewer than five options for Grade selection. Grades for Hepatic and hematologic are based on numerical lab values relative to normal values for that lab. See below.

Refer to the tables on the following pages for detailed information on the evaluation, grading and management for specific types of adverse events.

Drug interaction

Symptoms	• Various symptoms related to specific medications involved.
Medical History	• According to specific medications involved & symptoms.
Investigations	• According to specific medications involved & symptoms. Important to measure drug levels or assess drug effects.
Grading severity	• Grade 1: Potential drug interaction noted but no change in therapy required and neither short- nor long-term effects detected. • Grade 2: Potential drug interaction is noted and after an initial change in therapy no further problems. Subject does not suffer any untoward clinical effect. OR Drug interaction is noted and therapy has to be modified repeatedly but eventually is successful. Subject does not suffer any untoward clinical effect. • Grade 3: Drug interaction noted. Care providers unable to adjust therapy successfully to achieve therapeutic effects. No other adverse effect. • Grade 4: Drug interaction causes serious health problems such as diabetes or hypertensive, or cardiac crisis or results in seizures.
Management	• Grade 1-2: Continue monitoring. • Grade 3 or 4: LTBI therapy must be discontinued.

Gastrointestinal intolerance

Symptoms	• Nausea, Upset stomach, Vomiting • Loss of appetite • Abdominal pain • Diarrhea

Medical History	Subject must be questioned regarding • Alcohol • Past history of other gastrointestinal (GI) problems particularly peptic ulcer or gallbladder disease. GI intolerance must be distinguished from other GI problems including gallbladder (cholecystitis), appendicitis, peptic ulcer, etc. • Use of other potentially causative medications. • Females of childbearing age should be questioned carefully to rule out pregnancy. Physical examination required • Vital signs: temperature, heart rate and blood pressure. • Abdominal exam for signs of peritoneal irritation, tenderness, or mass.
Investigations	• Liver function test (bilirubin, ALT, AST) • Amylase • CBC • Pregnancy test (women of childbearing age) • Abdominal/ Liver ultrasound or X-rays may be performed at discretion of treating team.
Grading severity	• Grade 1: Some upset stomach with nausea and/or loss of appetite but no vomiting and no change in bowel habits. • Grade 2: Nausea with some vomiting, or abdominal pain that is severe enough to disturb daily routine, or persistent diarrhea. • Grade 3: Prolonged nausea and vomiting and/or severe abdominal pain that disrupts daily life (e.g. cannot sleep) severe diarrhea (5 or more BM's/day).
Management	• Grade 1: Change the hours of treatment. Therapy can be taken with meals. • Grade 2: Gravol or other anti-emetic may be given. Try changing the hours of treatment and taking the pills with meals. Take one or two days off all therapy and then try again. A lower dose for the first two to three days may be tried (then resume normal dose). (If this strategy is used, then subject therapy must be prolonged by the total number of days with no or reduced therapy. This interruption is not counted in the calculation of subject compliance.) • Grade 3: Gravol or other anti-emetic may be given. If unsuccessful, stop medication.

Hematologic

Symptoms	• Usually no symptoms, picked up by measuring hematologic parameters.
Medical History	• As necessary, question regarding other medications and diet (particularly if iron deficiency is possible). For females of childbearing age, question regarding menstrual period (heaviness, frequency). • Also question regarding alcohol and use of other possible hematologic suppressants.
Investigations	• B12, folate and iron studies • CBC & differential • Other investigations may be needed

Grading severity	• Grade 1: Neutrophils ≥ 1500/mm3 and < lower limit of normal (LLN) or ≥ 1.5 x 10e9 /L and < LLN OR Platelets ≥ 75,000/mm3 and < LLN or ≥ 75.0 x 10e9 /L and < LLN. • Grade 2: Neutrophils ≥ 1000 and < 1500/mm3 or ≥ 1.0 and <1.5 x 10e9 /L OR Platelets ≥ 50,000 and < 75,000/mm3 or ≥ 50.0 and < 75.0 x 10e9 /L. • Grade 3: Neutrophils ≥ 500 and <1000/mm3 or ≥ 0.5 and <1.0 x 10e9 /L OR Platelets <50,000 and ≥ 25,000/mm3 or < 50.0 and ≥ 25.0 x 10e9 /L. • Grade 4: Neutrophils <500/mm3 or <0.5 x 10e9 /L OR Platelets < 25,000/mm3 or < 25.0 x 10e9/L.
Management	• Grade 1-2: Continue monitoring. • Grade 3 or 4: Review with treating team, evaluate other causes. If no other cause is found and not corrected with B12, folate or iron, discontinue therapy.

Hepatotoxicity

Symptoms	• Anorexia, loss of appetite • Fatigue • Nausea and vomiting • Right upper quadrant pain • Jaundice, dark urine, pale stools • Itching • May have easy bruising, leg edema or abdominal swelling
Medical History	Study subject must be questioned regarding • Alcohol • Use of recreational drugs, prescription, non-prescription drugs & herbal remedies • Past history of liver disease • Injection drug use, transfusions and other risk factors for liver disease Physical examination • Assess the presence of jaundice. • Examine liver for tenderness, enlargement and signs of liver failure (bruising, bleeding, edema and ascites).
Investigations	• Liver function test (bilirubin, ALT, AST) • CBC, INR • HIV, Hepatitis A, B and C serology (unless known positive) • Abdominal / Liver ultrasound may be performed at discretion of treating tea,
Grading severity	• Grade 1-2: ALT/AST 1 to ≤ 3 times upper limit of normal (ULN) plus symptoms as above **OR** ALT/AST 1 to ≤ 5 times ULN and no symptoms. • Grade 3: ALT/ AST 3 to ≤ 10 times ULN plus symptoms as above **OR** ALT/AST 5 to ≤ 10 ULN and no symptoms. • Grade 4: ALT or AST > 10 times ULN.

Management	• Grade 1-2: Therapy should be continued, LFT's should be repeated in 2 weeks. • Grade 3 or 4: Therapy should be discontinued permanently unless there is another explanation for the hepatotoxicity. Follow-up should include ALT and AST approximately weekly until the values return to normal (at least 3 LFT's).

Pregnancy

Symptoms	• Nausea, upset stomach, vomiting • Loss of appetite
Medical History	Subject must be questioned regarding • Sexual activity and contraceptive use • Date of last menstrual period
Investigations	• Pregnancy test
Grading severity	• Grade 3: an unintended pregnancy is considered a grade 3 adverse event
Management	• Stop study drug and consider restarting therapy following completion of the pregnancy.

Rash

Symptoms	• Itching, rash or hives • Location – may be generalized or localized - does it affect limbs, trunk, or face? - is it discrete spots or confluent? - what percentage of total body area is affected? • May cause low blood pressure and weakness, dizziness, or fever. • May cause painful mouth ulcers, eye irritation, wheezing/shortness of breath.
Medical History	Subject must be questioned regarding • Use of drugs including non-prescription drugs, herbal remedies and recreational drugs. • The relationship of the rash to timing of the when medication is taken. • Exposure to other potential allergens, especially food. • Past history of allergies and family history of allergies. Physical examination • Location of the rash: face, trunk (back, stomach, or chest), and limbs. • Appearance of the rash: color (red, purplish, etc.), markings (small spots or large patches), palpable, hives or purpura? • Vital signs: blood pressure and heart rate, and temperature. • Mucus membranes and respiratory system must be examined carefully.
Investigations	• CBC and differential with specific count of eosinophils. • Flow rates (if wheezing is present).
Grading severity	• Grade 1: Itching only, or rash is limited to limbs, or trunk, or face only. Vital signs, mucosal, conjunctiva – all normal. • Grade 2: Rash affects limbs and trunk, or **more than 50%** of total body surface area or is **confluent** in areas. Vital signs mucosa conjunctiva – all normal. • Grade 3: Rash affects 100% of body surface area or mucus membranes, or conjunctiva are affected, or vital signs are abnormal (fever or low blood pressure), or there is wheezing.

Management	• Grade 1: May continue therapy. Give antihistamines. Close follow-up required (daily or every other day). If the rash worsens, management is re-evaluated. • Grade 2: Stop therapy. Give antihistamines. Close follow-up. May re-challenge. • Grade 3: Permanent discontinuation of therapy. Give antihistamines. May need steroids. Follow-up until resolved. Do not re-challenge.

PART 3: DETAILS OF SITE TRIAL TRAINING, MONITORING AND SUPERVISION.

Good Clinical Practice training:
All research staff at all sites completed GCP training, given by a certified GCP trainer, in their own countries. This was completed prior to beginning the adult trial, with the exception of the Benin site, where this training was given only before the pediatric trial started. GCP refresher training was repeated every two years at some sites. Project coordinator from the coordinating center reviewed the GCP with all staff when the initial training was done at all sites.

Initial training
Site investigators and research project coordinators were trained in the adult RCT in Montreal at a two days meeting in July 2009, prior to initiation at any site. Site investigators and research project coordinators were trained in the pediatric RCT in Montreal at a one day meeting in June 2011.
Site initiation training visits were conducted by the senior project coordinator at all sites, after ethics approval at each site. These visits were two weeks duration at all international sites, and of 3-4 days duration in Canadian sites. This included a tour of the clinical locations, research offices, recruitment offices, laboratories, pharmacy etc. Review Good Clinical Practice. Site start-up procedure and requirements. Review protocol (primary and secondary outcomes, inclusion/exclusion criteria, screening, recruitment, consent and follow-up (Compliance, AEs, active TB etc).
Training included classroom teaching, practical teaching (TST administration and reading) then working with site staff to identify eligible persons, approach and enroll them, randomize and initiate study therapy.
Site initiation training visits for the pediatric trial was also conducted by the senior project coordinator at all sites. This took only 1-2 days, and was performed during a monitoring visit for the adult trial.

Monitoring:
Site monitoring visits for the adult and pediatric trials were conducted approximately every 6 months at all sites. These were 1 week duration at all international sites and two days duration at Canadian sites. Initially these visits were to monitor only the adult site, but once the pediatric trial started, this trial was monitored during the same site visits.

Activities of each monitoring visit:
In brief, during each visit the monitors would first meet the site investigators, review progress, answer all questions/issues they have, plus review outstanding issues raised in the last visit. Then meet the team and discuss any issues and answer their questions, and make sure all procedures/protocol of the RCT study are well understood and properly followed. All participant files recruited since the last monitoring visit were reviewed to ensure all CRFs (Screening & Randomization form, Follow-up during treatment, End of treatment, Follow-up post treatment, Adverse Event initial and final, Active TB initial and Final) are properly completed and accurate when checked against the original source documents. Ensure that all Inform Consent Form/Assent/Parental are signed/dated by patient and research staff. Storage and quantity of Medications (INH/RIF) and Tuberculin (PPD) were verified at each visit to ensure proper storage and that they had sufficient supplies. Meeting with all members of the site team at the end of the visit to review the findings. A monitoring visit report was sent to the site after each visit. (see "SOP Monitoring site visit" for more details).

Specific items reviewed/activities:
Master Binder (essential documents): Reviewed the master binder at each visit to make sure all the trial related documents needed were up to date. This included all versions of the study protocol, initial and continuation approval from their ethics committees, the task delegation log, the CV's of all new staff who works on the study.
Screening log – Verify the screening book (log) to see how many patients were eligible, accepted to participate to the study and how many refusals. A complete count was made each visit.
Master identification log – All participants who were randomized were recorded on this list. Ensure that it is complete, matches the informed consents, and also ensure that list was kept confidential and not with the participant study files.
All informed Consent Forms for adults, and all parental consent and child's Assent forms for pediatric study: All informed consent forms of all participants enrolled since the previous monitoring visit were reviewed at each visit to ensure they were signed and dated properly – by the participant and the research staff. Also verified that all consent forms were stored properly in secure area and under lock and key.
Identification form: Identification form (information form with the participants' full names, addresses, phone numbers etc) were reviewed to ensure all were properly completed and attached to the informed consent form.
Eligibility: Eligibility was verified for all participants enrolled since the previous monitoring visit. This review was based on initial case report forms, plus source documents including Chest X-ray reports, initial laboratory tests, and TST readings.

Participant records – if had an adverse event or active TB: the files of all participants who had adverse events, or had been diagnosed to have active TB since the last visit were reviewed carefully, to ensure the study protocols for investigation, management and reporting of these events were followed. As well all information in the source documents was cross-verified with the web-based forms to ensure accurate entry of this data.

Participant study files: All participant files who were enrolled in the study since the previous visit were reviewed to ensure that all the case report forms (CRF) were properly completed for each participant, and every data point compared with the data entered in the web-based forms. A minimum of 10 files were reviewed; if more than 10 participants had been enrolled since the last visit, then a random sample of files were reviewed with a minimum of a 10% sample reviewed. In addition prior to each site visit, the on-line data base was checked for missing or non-coherent data. If errors or missing information was detected, then these participant files were also reviewed. In addition to the file reviews, the PI from the coordinating center reviewed all randomization chest Xrays of participants who were enrolled in each trial since his last visit. All errors were reviewed with site staff

Monitoring report: After each visit performed, a monitoring visit report was sent to the site. The report included the methods of review, the observations and recommendations made by the coordination center. At the subsequent monitoring visit, we reviewed all recommendation from the previous visit to ensure they were followed. It was then mention in the report of the actual visit if recommendations were followed or not.

Number of monitoring visits to each site:

International

Australia: Principal Investigator (PI) 3 visits, Research coordinator from coordinating center 4 visits
Benin: Principal Investigator 3 visits, Research coordinator from coordinating center 12 visits, (3 with PI)
Brazil: Principal Investigator 3 visits, Research coordinator from coordinator center 6 visits
Ghana: Principal Investigator 3 visits, Research coordinator from coordinating center 6 visits,
Guinee: Principal Investigator 3 visits, Research coordinator from coordinating center 7 visits (1 with PI)
Korea: Principal Investigator 3 visits, Research coordinator from coordinating center 5 visits
Indonesia: Principal Investigator 7 visits, Research coordinator from coordinating center 3 visits (1 with PI)
Saudi Arabia: Principal Investigator 2 visits

Canada

Edmonton: Principal Investigator 2 visits, Research coordinator from coordinating center 6 visits,
Montreal: Research coordinator from coordinating center 6 visits
Saskatoon: Principal Investigator 3 visits, Research coordinator from coordinating center 5 visits
Vancouver: Principal Investigator 3 visits, Research coordinator from coordinating center 9 visits, (1 with PI)

Ensuring data quality:

Case report forms: Standard Operating Procedures (SOPs) were created for each CRF form and sent to all sites.

Website initial CRF: In order to randomize a participant, the study staff had to enter the full initial case report form on-line. Eligibility was verified by this web-site and then randomization performed. In this way, missing information was minimized and all those randomized were truly eligible.

Adverse event: When a site had a participant with an adverse event, they had to complete the adverse event initial form on the wed data base within 48hrs. When this was completed the coordinating center received an automatic email from the web data base system that a new AE had occurred. The research coordinator (who was unblinded) at the coordinating centre responsible for all Adverse Events contacted the site to get more detail about the AE (was it serious, and if so was it expected or unexpected). This coordinator assisted sites to follow the AE investigation and management protocols and to judge if serious and/or unexpected. A detailed description of the event was written by the site and reviewed by the research coordinator who was unblinded. A SOP was created to help sites classify the AE – this was adapted from ATS guidelines for hepato-toxicity (Saukonnen et al), and the National Cancer Institute Common Terminology Criteria for Adverse Events v2.0 & v4.02 (http://ctep.info.nih.gov/reporting/ctc.html) for all other types of AE. This report was then blinded (all reference to study drug removed) and then reviewed, in blinded fashion, by the principal investigator, to ensure the AE did not meet criteria for serious and unexpected. (Serious and unexpected AE were notified to the Data Safety and Monitoring Board immediately). Once the adverse event had resolved, then the sites completed the adverse event final form. This was reviewed by the coordinator for blinding, and then the PI for completeness, and finally the AE report was made available to the 3 members of the adverse event panel. These 3 members evaluated each adverse event report independently and blinded to the regimen.

Note that the PI also remained blinded to study drug at all of these steps, but the research coordinator was always unblinded in order to be able to assist the sites.

Active TB: When a participant was suspected to have an active TB, the site had to complete the active TB initial form on the web data base within 24hrs. The coordinating center received an automatic email from the web data base system that a suspected active TB had occurred. The research coordinator from the coordinating center responsible for Active TB (who was unblinded at all times) contacted the site to get more details, and to make sure they followed the protocol for investigation and management of active TB. Sites sent CXR pictures if applicable, and a detailed description of the suspected active TB event was written by the site and reviewed by the research coordinator (unblinded) to make sure all information was included. Once active TB treatment was completed, and end of treatment information (X-rays and TB smear and cultures) gathered, the site completed the final active TB form. This report was then blinded by removing all reference to study therapy, and reviewed, along with all relevant X-rays by the principal investigator at the coordinating site. If all information needed was available, then the full details was reviewed by 3 members of the Clinical Panel, who evaluated each case independently and blinded to the regimen. Note that the PI remained blinded to study drug at all steps, but the research coordinator was always unblinded in order to be able to assist the sites.

Monitoring data quality

Mostly reviewing all participant files that have missing information or correction to do, when revision from the web database was done before the visit. Ensure that all the CRF form were properly completed for each participant.

Data from study: All CRFs (Screening & Randomization initial data form, Follow-up during treatment, End of treatment, Follow-up post treatment, Adverse Event initial and final, Active TB initial and Final) who were entered into a web data base. The coordinating center revised all data entered before each site visit to make sure there is no mistake, typo or missing information. Findings were sent to site to have them corrected and were revised during site visit. If site visit was not done at site, data were revised every 6 months (approx..) and finding were sent to the sites to have them corrected/entered the information.

Follow-up during treatment: reviewed all data that has been input into the website to identify missing data and any potential errors.

Closing subject files – final data quality check: Once a participant's follow-up period was completed (i.e. 28 months post-randomization), the site reviewed all the collected information by comparing this with the web-site data. Once each file was reviewed, it was anonymized to ensure confidentiality, and stored.

Closing study Site – Final: Coordinating center close the study site and ensure site closeout of clinical trial sites participating in this study. Ensure that all participant files, inform consent form and master binder (essential documents) are stored properly in a secure room (double lock) and accessible if further information is needed. This is in process at the moment.

Standard Operating Procedures: Monitoring site visit Procedures

1. General information

1.1 The purpose of study monitoring is to verify that:

- The rights and well-being of human subjects are protected.
- Reported study data are accurate, complete, and verifiable from source documents.
- The study is conducted in compliance with the currently approved protocol, and GCP.

1.2 The monitor should visit the study site frequently enough to assure that:

- The facilities used continue to be acceptable for purposes of the study.
- The study protocol or investigational plan is being followed.
- Changes to the protocol have been approved by the IRB.
- Accurate, complete, and current records are being maintained.
- The investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.

2. Co-ordinating Centre Preparation for a Monitoring Visit

2.1 Review relevant study site data using ACCESS programs for data monitoring and recent data dump from TBERA (request from Web Team) to identify any issue with the data. Also look for any unusual trends in the data. (Refer to Appendix 1 for details)

2.2 Review prior monitoring report and identify any outstanding issues.

2.3 Ensure all Note-To-Files have been completed.

2.4 Review emails from study site for any outstanding issues.

2.5 Review adverse events and active TB cases to identify any outstanding issues.

2.6 Arrange an appropriate time for the monitoring visit with the study site, ensuring the availability of the Site Investigator and Study Site Coordinator.

2.7 Based on the points above decide on objective of visit and data to be reviewed then prepare an email to announce the Study Site Monitoring visit including a draft agenda (refer to Appendix 2 for details)

3. The Monitoring Visit

3.1 Meet with the study team, review and adjust the agenda, and discuss any issues.

3.2 Verify all consent forms for study subjects enrolled since last visit.

3.3 Verify that all study subject records, data and source documents identified to be reviewed during the monitoring visit are complete and accurate.

3.4 Verify any adverse events or active TB cases to make sure all information needed was obtained. Take pictures of the CXRs of Active TB case if needed because site doesn't have digital CXR.

3.4 Verify that essential documentation of the study, required by the monitoring visit, is complete (i.e. recent correspondence, subject screening log, subject identification code lists, up-to-date medical and nursing licenses, task delegation log and documents related to the management of study drugs as applicable).

3.5 Verify any relevant study biological specimens, their storage and documentation.

3.6 Verify that any relevant study drug inventories are accurate and study drugs are stored appropriately.

3.7 Verify that all study documents are kept in a secure, confidential manner.

3.8 Ensure Monitoring Visit Log (refer to Appendix 3) is signed by monitor and all relevant study personnel.

3.9 Summary meeting with all study team at the end of the monitoring visit.

4. Following the Monitoring Visit

4.1 Prepare a site visit monitoring report detailing monitoring findings and send to study site investigator (refer to Appendix 4 for details). The report should include a statement of the findings, conclusions and any actions required to correct any deficiencies noted during the visit.

4.2 Follow-up with the study site to ensure all corrective actions have been taken.

References

Guidance for Industry. Good Clinical Practice: Consolidated Guideline. ICH Topic E6

PART 4: SUPPLEMENTAL TABLES 1-8

Supplement Table S1: Description of patient characteristics by arm in the Phase 2 and Phase 3 trials combined *(Phase 2 participants separately described in Menzies 2008[16])*

Characteristic	9INH[1] (n=3,416)	4RIF[1] (n=3,443)	Total (n=6,859)
	N (%)	N (%)	N (%)
Center, N (%)			
Australia	91 (2.7)	100 (2.9)	191 (2.8)
Benin	574 (16.8)	576 (16.7)	1,150 (16.8)
Brazil	506 (14.8)	499 (14.5)	1,005 (14.7)
Canada	866 (25.4)	855 (24.8)	1,721 (25.1)
Ghana	181 (5.3)	187 (5.4)	368 (5.4)
Guinea	428 (12.5)	444 (12.9)	872 (12.7)
Indonesia	432 (12.6)	423 (12.3)	855 (12.5)
Korea	285 (8.3)	300 (8.7)	585 (8.5)
Saudi Arabia	52 (1.5)	59 (1.7)	111 (1.6)
SEX			
Male n (%)	1,479 (43.3)	1,426 (41.4)	2,905 (42.4)
Female n (%)	1,936 (56.7)	2,017 (58.6)	3,953 (57.6)
Age			
Mean - in years (SD)	38.1 (13.7)	38.0 (13.8)	38.1 (13.7)
18-35 year, n (%)	1,652 (48.4)	1,667 (48.4)	3,319 (48.4)
36-50 years, n (%)	1,086 (31.8)	1,098 (31.9)	2,184 (31.8)
51-90 years, n (%)	677 (19.8)	678 (19.7)	1,355 (19.8)
Height, weight, BMI	**median (Q1, Q3)**	**median (Q1, Q3)**	**median (Q1, Q3)**
Height (m), median (Q1, Q3)	1.6 (1.6 - 1.7)	1.6 (1.6 - 1.7)	1.6 (1.6 - 1.7)
Weight (kg), median (Q1, Q3)	64.0 (55.0 - 74.0)	64.0 (55.0 - 74.1)	64.0 (55.0 - 74.0)
BMI, median (Q1, Q3)	23.9 (21.0 - 27.0)	24.0 (21.0 - 27.1)	24.0 (21.0 - 27.1)

Characteristic	9INH[1] (n=3,415)	4RIF[1] (n=3,443)	Total (n=6,858)
	N (%)	N (%)	N (%)
TST reaction size (mm), n(%)			
5-9 mm	332 (9.9)	325 (9.6)	657 (9.7)
10-14 mm	1,234 (36.7)	1,236 (36.4)	2,470 (36.5)
>=15 mm	1,799 (53.5)	1,837 (54.1)	3,636 (53.8)
TST not done – IGRA positive	50	45	95
Risk Factor (indication for treatment)			
HIV infected	130 (3.8)	125 (3.6)	255 (3.7)
Close contact	2,251 (65.9)	2,208 (64.1)	4,459 (65.0)
Casual contact	377 (11.1)	423 (12.3)	800 (11.7)
Immune-suppressive condition or therapy (Diabetes, TNFa, Renal Failure)	107 (3.1)	109 (3.2)	216 (3.1)
Upper lobe fibronodular disease with area >2 cm²	10 (0.3)	12 (0.3)	22 (0.3)
TST converter	28 (0.8)	30 (0.9)	58 (0.8)
Combined risk factors			
TST 10-14 mm, and with 2 of 4 factors:[2,3]	67 (2.0)	89 (2.6)	156 (2.3)
TST ≥ 15mm or QFT positive and with 1 of 4 factors:[3]	445 (13.0)	447 (13.0)	892 (13.0)
Chest X-ray result			
Normal	2,647 (77.5)	2,633 (76.5)	5,280 (77.0)
Apical/upper lobe fibronodular disease >2 cm²	89 (2.6)	88 (2.6)	177 (2.6)
Apical/upper lobe fibronodular <2 cm²	128 (3.7)	134 (3.9)	262 (3.8)
Granulomas	145 (4.2)	154 (4.5)	299 (4.4)
Costo-phrenic angle blunting or apical pleural caps	21 (0.6)	25 (0.7)	46 (0.7)
Other possible TB-related	56 (1.6)	68 (2.0)	124 (1.8)
Hilar lymph node enlargement	48 (1.4)	58 (1.7)	106 (1.5)
Abnormality not TB related	281 (8.2)	283 (8.2)	564 (8.2)

Notes:

1. Percent are calculated based on the total in MITT analysis
2. Of the 156 patients in this group, 14 who were enrolled in Phase 2, had TST of 5-9mm.
3. The 4 factors were: Born in or living in country with TB incidence >100/100,000; Aboriginal Canadian living on reserve, BMI < 19, Abnormal CXR consistent with past TB-infection (Upper lobe fibronodular disease with area <2 cm² or granulomas, or calcified hilar lymph nodes, or costo-phrenic angle blunting, or apical cap). Abbreviations: **SD** standard deviation; **BMI** Body mass index; **m** metres; **kg** kilograms; **IGRA** : Interferon Gamma release Essay; **Q1** : first quartile; **Q3**: third quartile**; TNFa:** tumor necrosis factor alpha, **TST:** tuberculin skin test.

Supplement Table S2: Completion of treatment (MITT) (secondary end-point) in the Phase 2 and Phase 3 trials combined.
(*Completion of study therapy by Phase 2 participants only is described in Menzies 2008*[16])

	9INH[1] N (%)	4RIF[1] N (%)	Risk Difference[2] (4RIF- 9INH in %, 95%CI)	P value*
Total in MITT analysis	3,416	3,443		
Treatment Completed (took at least 80% of doses)	2144 (62.8)	2710 (78.7)	15.6% (13.4, 17.8)	<0.001
Treatment Completed within allowed time (**per protocol**)	1931 (56.5)	2411 (70.0)	13.0% (10.6, 15.3)	<0.001
Treatment completed but NOT within time allowed by protocol	213 (6.2)	299 (8.7)	2.5%	
Treatment not-completed (total: all reasons)	1272 (37.2)	733 (21.3)	-15.9%	
Death during treatment (not related to therapy)	4 (0.1)	0 (0.0)	-0.1%	
Never started (patient decision) (includes 1 death)	210 (6.2)	163 (4.7)	-2.5%	
Therapy stopped permanently for all Grade 1-4 AE (and had not already completed)	168 (4.9)	85 (2.5)	-2.4%	
Therapy stopped permanently for Grade 3-4 AE (and had not already completed)	108 (3.1)	45 (1.3)	-1.8%	
Started but patient decided to stop treatment (includes patients stopped for AE, and restarted, then later dropped out)	890 (26.1)	485 (14.1)	-12.0%	
• Took 50-79% of doses	221 (6.5)	141 (4.1)	-2.4%	
• Took 1-49% of doses	669 (19.6)	344 (10.0)	-9.6%	

Notes:
1. Percent are calculated based on the total MITT analysis
2. The risk difference and p value were calculated using a binomial distribution model with an identity link, accounting for correlation of different patients coming from the same family.

Supplemental Table S2b: Use of Alternative LTBI regimen (Phase 3 only)

Reason for Stopping study drug	Number starting Alternative regimen (by original study drug)		
	9INH	4RIF	Total
Never Started	**2**	**5**	**7**
Patient decision (non-adherence)	**14**	**7**	**21**
Adverse Event	**41**	**22**	**63**
TOTAL	**57**	**34**	**91**

Supplement Table S3: Occurrence of adverse events [1] (secondary end-point) – Phase 2 & 3 combined. (Adverse events of *study therapy among Phase 2 participants only is described in Menzies 2008[16]*)

	9INH[2] N (%)	4RIF[2] N (%)	Risk Difference[3] (4RIF- 9INH in %, 95%CI)	P value[3]
Total in MITT analysis	3,416	3,443		
Total taking at least one dose of therapy	3,205	3,280		
Total events reviewed by DSMB panel	202 (6.3)	108 (3.3)	-3 (-4.1, -2.0)	<0.001
Study drug restarted successfully				
Grade 1-2 AE, and study drug restarted without recurrence of symptoms	18 (0.1)	14 (0.2)	0 (-0.2, 0.2)	0.768
Grade 3-4 AE and study drug restarted without recurrence of symptoms (includes 3 with pregnancy)	5 (0.2)	1 (0.0)	-0.1 (-0.3, 0.0)	0.099
Study drug stopped permanently - Total	179 (5.6)	93 (2.8)	-2.9 (-3.9, -1.9)	<0.001
Grade 1-2 AE.	60 (1.9)	40 (1.2)	-0.8 (-1.5, -0.1)	0.017
Grade 3 - Pregnancy only (Of these Panel judged only 4 were likely related to study drug) [4]	41 (1.3)	23 (0.7)	-0.6 (-1.1, -0.1)	0.015
All other Grade 3-5 AE (non-pregnancy)[5]	78 (2.3)	30 (0.9)	-1.5 (-2.1, -0.9)	<0.001
All Grade 3-4 Hepatotoxicity[6]	66 (2.1)	11 (0.3)	-1.7 (-2.3, -1.2)	<0.001
All Grade 5 - Death	4 (0.1)	0 (0.0)	-0.1 (-0.3, -0.0)[7]	0.045
Study drug stopped permanently for Grade 3-5 AE, AND judged by panel as possibly/probably related to study drug				
Grade 3-5 AE of all types	75 (2.3)	31 (0.9)	-1.4 (-2.0, -0.8)	<0.001
Grade 3-4 Hepatotoxicity	65 (2.0)	11 (0.3)	-1.7 (-2.2, -1.2)	<0.001
Grade 5 deaths	1 (0.0)	0 (0.0)	0 (-0.1, 0.0)[7]	0.317
Grade 3-5 adverse events with study drug stopped permanently, that occurred in first 146 days post randomization				
Grade 3-5 AE of all types - whether panel judged related to study drug or not	87 (2.7)	53 (1.6)	-1.1 (-1.8, -0.4)	0.002
Grade 3-5 AE of all types – but only those judged by panel as possibly/probably related to study drug	64 (2.0)	31 (0.9)	-1.1 (-1.6, -0.5)	<0.001
Grade 3-4 hepatoxicity – (all that occurred were judged by AE panel as possibly/probably related to study drug)	54 (1.7)	11 (0.3)	-1.4 (-1.8, -0.9)	<0.001

Notes:

1. All adverse events were reviewed by a 3-member independent review panel who were blinded to study drug. See supplement for detailed protocol re AE management and grading. Severity was graded according to published criteria: from the American Thoracic Society for hepatoxicity [19], and from the National Cancer Society for all other events [20].
2. Percent are calculated based on the total number of participants taking at least one dose of study drug.
3. The risk difference and p value were estimated using a binomial distribution model with an identity link via GEE. An exchangeable correlation structure and robust standard errors were used to account for correlation of different patients coming from the same family. P values not estimated for events judged Not AE, or not related to study drugs.
4. Pregnancy considered possibly/probably related to study by independent panel if participant was taking hormonal contraception, and conception occurred after start of study drug, up to 1 month after end of study drug. This includes six who

had already completed >80% of doses by the time the pregnancy was recognized. Shown as completed in Table 2, but included here.

5. Four participants had a Grade 3-4 AE related to study drug, but had already completed medication (>80%). Shown as completed in Table 2, but included here.

6. For details of other types of adverse events see Supplement Table 4

7. 95% CI estimated using method suggested by Newcombe (Newcombe, RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998;17(8):873-90).

Supplement Table S4: Type of adverse events (Grade 3-5 and considered possibly or probably related to study drug by AE review panel [1]) – Phase 2 and 3 combined (*Types of adverse events with study therapy by Phase 2 participants only is described in Menzies 2008[16]*)

	9INH[2] N (%)	4RIF[2] N (%)	Risk Difference[3] (4RIF- 9INH in %, 95%CI)	P value
Total randomized (MITT)	3,416	3,443		
Total taking at least one dose of therapy	3,205	3,280	---	
Total Grade 3-5 Adverse events judged possibly or probably due to study drugs	75 (2.3)	31 (0.9)	-1.4 (-2.0, -0.8)	<0.001
Rash or other allergy	2 (0.1)	6 (0.2)	0.1 (-0.1, 0.3)	0.163
Drug Interaction	0 (0.0)	2 (0.1)	0.1 (-0.1, 0.2)	0.5
Hepato-toxicity	65 (2.0)	11 (0.3)	-1.7 (-2.2, -1.2)	<0.001
GI intolerance	1 (0.0)	3 (0.1)	0.1 (-0.1, 0.2)	0.326
Hematologic	0 (0.0)	6 (0.2)	0.2 (0.1, 0.3)	0.031
Pregnancy[4]	2 (0.1)	2 (0.1)	0 (-0.1, 0.1)	0.983
Other AE	4 (0.1)	1 (0.0)	-0.1 (-0.2, 0.0)	0.174
Death[5]	1 (0.0)	0 (0.0)	0 (-0.1, 0.0)	0.317

Notes:

1. All adverse events were reviewed by a 3-member independent review panel who were blinded to study drug. Severity was graded according to published criteria: from the American Thoracic Society for hepatoxicity [19], and from the National Cancer Society for all other events [20].

2. Percent are calculated based on the total number of patients that took at least one dose of therapy

3. The risk difference and p value were calculated using a binomial distribution model with an identity link, accounting for correlation of different patients coming from the same family. If zero events, the 95% CI were estimated using method suggested by Newcombe.

4. Pregnancy considered possibly/probably related to study by independent panel if participant was taking hormonal contraception, and conception occurred after start of study drug, up to 1 month after end of study drug.

5. Death judged possibly related to study by two panel members and unlikely related by one.

Supplemental Table S5: Comparison of patient characteristics of all who completed vs did not complete study therapy (Phase 3 only)

Characteristic	All completed	All non-completed	P values
	N=4,272	N=1,740	
AGE: Mean (SD), n (%)	38.9 ± 13.8	37.2 ± 14.0	<0.001
18-35 years,	1,915 (44.8)	905 (52.0)	<0.001
36-50 years,	1,438 (33.7)	513 (29.5)	0.002
51-90 years,	919 (21.5)	322 (18.5)	0.009
SEX: Male n (%)	1,772 (41.5)	688 (39.5)	0.166
Female n (%)	2,500 (58.5)	1,052 (60.5)	0.166
Height (m), median (Q1, Q3)	1.6 (1.6, 1.7)	1.6 (1.6, 1.7)	0.328
Weight (kg), median (Q1, Q3)	64.0 (55.0, 74.0)	63.0 (55.0, 73.0)	0.133
BMI, median (Q1, Q3)	24.0 (21.0, 27.0)	23.6 (21.0, 27.0)	0.432
TST Reaction: 5-9 mm	430 (10.2)	184 (10.7)	0.551
10-14 mm	1,555 (37.0)	633 (37.0)	0.997
≥15 mm	2,220 (52.8)	895 (52.3)	0.718
Risk Factor (indication for treatment)	**N (%)[1]**	**N (%)[1]**	
HIV infected	208 (4.9)	34 (2.0)	<0.001
Close contact of confirmed active TB: [2]	2,993 (70.1)	1,255 (72.1)	0.111
Casual contact of confirmed active TB	500 (11.7)	246 (14.1)	0.009
Other Immune-suppressive condition or therapy (Diabetes, TNFa inhibitor therapy, Renal Failure)	143 (3.3)	52 (3.0)	0.476
Upper lobe fibronodular disease with area ≥2 square cm	7 (0.2)	1 (0.1)	0.452
Combined risk factors			
TST 10-14 mm, and with 2 of 4 factors [3]	83 (1.9)	19 (1.1)	0.021
TST ≥ 15mm or IGRA positive, and with 1 of 4 factors [3]	338 (7.9)	133 (7.6)	0.726
Chest X-ray result			
Normal	3,275 (76.7)	1,440 (82.8)	<0.001
Apical/upper lobe fibronodular disease ≥2 square cm	130 (3.0)	28 (1.6)	0.002
Apical/upper lobe fibronodular disease <2 square cm	116 (2.7)	27 (1.6)	0.007
Granulomas	131 (3.1)	49 (2.8)	0.605
Costophrenic angle blunting	23 (0.5)	10 (0.6)	0.863
Hilar lymph node enlargement	90 (2.1)	12 (0.7)	<0.001
Other possible TB-related	93 (2.2)	31 (1.8)	0.328
Abnormal, but not TB related	414 (9.7)	143 (8.2)	0.074

Notes: P values were obtained by performing T-test (if normally distributed) or Wilcoxon two-sample test (if not normally distributed) or Chi-square analysis (Fish Exact test for cells number less than 5) for categorical variables

Supplemental Table S6: Comparison of patient characteristics of those lost to follow-up, vs completed 28 months follow-up (Phase 3 only)

Characteristic	All not lost to FU	All lost to FU	P values
	N=5,703	N=309	
AGE: Mean (SD), n (%)	38.5 ± 13.9	36.4 ± 14.1	0.004
18-35 years,	2,648 (46.4)	172 (55.7)	0.002
36-50 years,	1,867 (32.7)	84 (27.2)	0.042
51-90 years,	1,188 (20.8)	53 (17.2)	0.12
SEX: Male n (%)	2,326 (40.8)	134 (43.4)	0.369
Female n (%)	3,377 (59.2)	175 (56.6)	0.369
Height (m), median (Q1, Q3)	1.6 (1.6, 1.7)	1.6 (1.6, 1.7)	0.073
Weight (kg), median (Q1, Q3)	63.0 (55.0, 73.0)	62.0 (54.0, 74.0)	0.718
BMI, median (Q1, Q3)	24.0 (21.0, 27.0)	23.5 (20.5, 27.0)	0.186
TST Reactions: 5-9 mm	582 (10.4)	32 (10.5)	0.962
10-14 mm	2,072 (36.9)	116 (37.9)	0.729
≥15 mm	2,957 (52.7)	158 (51.6)	0.716
Risk Factor (indication for treatment), n(%)			
HIV infected	232 (4.1)	10 (3.2)	0.469
Close contact of confirmed active TB: [2]	4,043 (70.9)	205 (66.3)	0.087
Casual contact of confirmed active TB	704 (12.3)	42 (13.6)	0.517
Other Immune-suppressive condition or therapy (Diabetes, TNFa inhibitor therapy, Renal Failure)	180 (3.2)	15 (4.9)	0.101
Upper lobe fibronodular disease with area ≥2 square cm	7 (0.1)	1 (0.3)	0.345
Combined risk factors			
TST 10-14 mm, and with 2 of 4 factors [3]	95 (1.7)	7 (2.3)	0.427
TST ≥ 15mm or IGRA positive, and with 1 of 4 factors [3]	442 (7.8)	29 (9.4)	0.298
Chest X-ray result, n(%)			
Normal	4,464 (78.3)	251 (81.2)	0.219
Apical/upper lobe fibronodular disease ≥2 square cm	153 (2.7)	5 (1.6)	0.255
Apical/upper lobe fibronodular disease <2 square cm	132 (2.3)	11 (3.6)	0.162
Granulomas	171 (3.0)	9 (2.9)	0.931
Costophrenic angle blunting	29 (0.5)	4 (1.3)	0.087
Hilar lymph node enlargement	101 (1.8)	1 (0.3)	0.065
Other possible TB-related	115 (2.0)	9 (2.9)	0.28
Abnormal, but not TB related	538 (9.4)	19 (6.1)	0.052

Supplemental Table S7: Comparison of patient characteristics, among those who did NOT complete study therapy - by arms (Phase 3 only)

Characteristic	9INH	4RIF	P values
	N = 1,099	N=641	
AGE: Mean (SD), n (%)	37.0 ± 14.0	37.5 ± 14.2	0.431
18-35 years,	570 (51.9)	335 (52.3)	0.873
36-50 years,	327 (29.8)	186 (29.0)	0.745
51-90 years,	202 (18.4)	120 (18.7)	0.86
SEX: Male n (%)	443 (40.3)	245 (38.2)	0.39
Female n (%)	656 (59.7)	396 (61.8)	0.39
Height (m), median (Q1, Q3)	1.6 (1.6, 1.7)	1.6 (1.6, 1.7)	0.861
Weight (kg), median (Q1, Q3)	62.0 (55.0, 72.0)	63.0 (55.0, 73.0)	0.561
BMI, median (Q1, Q3)	23.5 (21.0, 27.0)	24.0 (21.0, 27.5)	0.319
TST Reactions: 5-9 mm	123 (11.3)	61 (9.7)	0.293
10-14 mm	409 (37.7)	224 (35.7)	0.394
≥15 mm	552 (50.9)	343 (54.6)	0.14
Risk Factor (indication for treatment), n(%)			
HIV infected	17 (1.5)	17 (2.7)	0.108
Close contact of confirmed active TB: [2]	824 (75.0)	431 (67.2)	<0.001
Casual contact of confirmed active TB	139 (12.6)	107 (16.7)	0.019
Other Immune-suppressive condition or therapy (Diabetes, TNFa inhibitor therapy, Renal Failure)	32 (2.9)	20 (3.1)	0.805
Upper lobe fibronodular disease with area ≥2 square cm	0(0.0)	1 (0.2)	0.368
Combined risk factors			
TST 10-14 mm, and with 2 of 4 factors [3]	11 (1.0)	8 (1.2)	0.632
TST ≥ 15mm or IGRA positive, and with 1 of 4 factors [3]	76 (6.9)	57 (8.9)	0.134
Chest X-ray result, n(%)			
Normal	907 (82.5)	533 (83.2)	0.74
Apical/upper lobe fibronodular disease ≥2 square cm	19 (1.7)	9 (1.4)	0.604
Apical/upper lobe fibronodular disease <2 square cm	11 (1.0)	16 (2.5)	0.015
Granulomas	33 (3.0)	16 (2.5)	0.538
Costophrenic angle blunting	7 (0.6)	3 (0.5)	0.754
Hilar lymph node enlargement	11 (1.0)	1 (0.2)	0.066
Other possible TB-related	18 (1.6)	13 (2.0)	0.553
Abnormal, but not TB related	93 (8.5)	50 (7.8)	0.628

Supplemental Table S8: Comparison of patient characteristics among all lost to follow-up, by arms (Phase 3 only)

Characteristic	9INH	4RIF	P values
	N=148	N=161	
AGE: Mean (SD), n (%)	35.2 ± 13.2	37.6 ± 14.9	0.2
18-35 years,	86 (58.1)	86 (53.4)	0.407
36-50 years,	42 (28.4)	42 (26.1)	0.651
51-90 years,	20 (13.5)	33 (20.5)	0.104
SEX: Male n (%)	69 (46.6)	65 (40.4)	0.268
Female n (%)	79 (53.4)	96 (59.6)	0.268
Height (m), median (Q1, Q3)	1.6 (1.6, 1.7)	1.6 (1.6, 1.7)	0.498
Weight (kg), median (Q1, Q3)	61.5 (54.0, 72.0)	65.0 (54.0, 75.0)	0.471
BMI, median (Q1, Q3)	23.4 (20.0, 26.3)	24.0 (21.0, 27.0)	0.095
TST REACTIONS: 5-9 mm	18 (12.2)	14 (8.9)	0.346
10-14 mm	58 (39.2)	58 (36.7)	0.655
≥15 mm	72 (48.6)	86 (54.4)	0.312
Risk Factor (indication for treatment), n(%)			
HIV infected	2 (1.4)	8 (5.0)	0.107
Close contact of confirmed active TB: [2]	102 (68.9)	103 (64.0)	0.358
Casual contact of confirmed active TB	19 (12.8)	23 (14.3)	0.711
Other Immune-suppressive condition or therapy (Diabetes, TNFa inhibitor therapy, Renal Failure)	8 (5.4)	7 (4.3)	0.666
Upper lobe fibronodular disease with area ≥2 square cm	0 (0.0)	1 (0.6)	1.000
Combined risk factors			
TST 10-14 mm, and with 2 of 4 factors [3]	2 (1.4)	5 (3.1)	0.451
TST ≥ 15mm or IGRA positive, and with 1 of 4 factors [3]	15 (10.1)	14 (8.7)	0.665
Chest X-ray result, n(%)			
Normal	124 (83.8)	127 (78.9)	0.270
Apical/upper lobe fibronodular disease ≥2 square cm	2 (1.4)	3 (1.9)	1.000
Apical/upper lobe fibronodular disease <2 square cm	3 (2.0)	8 (5.0)	0.223
Granulomas	4 (2.7)	5 (3.1)	1.000
Costophrenic angle blunting	2 (1.4)	2 (1.2)	1.000
Hilar lymph node enlargement	0 (0.0)	1 (0.6)	1.000
Other possible TB-related	4 (2.7)	5 (3.1)	1.000
Abnormal, but not TB related	9 (6.1)	10 (6.2)	0.962