U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	21024
Supplement #:	11
Drug Name:	Priftin® (rifapentine)
Indication(s):	Treatment of Latent Tuberculosis Infection
Applicant:	Sanofi Aventis
Date(s):	5/30/2014 (received); 11/30/2014 (PDUFA)
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Biometrics Division:	Division of Biometrics IV
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Keywords: Open-label, non-inferiority design, NDA review

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LIST OF ABBREVIATIONS

DSMB-Data Safety and Monitoring Board
LTBI-Latent Tuberculosis Infection
DOT-Directly-Observed Treatment
RPT-Rifapentine
INH-Isoniazid
MITT-Modified Intent-to-Treat
PY-Person Years
TST-Tuberculin Skin Test
CDC-Centers for Disease Control and Prevention
TBTC- Tuberculosis Trials Consortium
NIAID-National Institute of Allergy and Infectious Diseases
CDISC-Clinical Data Interchange Standards Consortium
ADaM-Analysis Data Model
SDTM-Study Data Tabulation Model
DAIP- Division of Anti-Infective Products
TEAE-Treatment-Emergent Adverse Event
NI-Non-Inferiority

1 EXECUTIVE SUMMARY

Priftin® (rifapentine) was originally approved for marketing in 1998 for treatment of active pulmonary tuberculosis (TB). The applicant submitted this supplemental New Drug Application seeking approval for an additional indication of treatment of latent TB infection (LTBI) caused by *Mycobacterium tuberculosis* in adults and children ≥2 years of age who are at risk of progression to TB disease (including those in close contact with an active TB patient, recent conversion to positive tuberculin skin test, HIV-infected subjects, or those with pulmonary fibrosis on radiograph). The primary source of evidence supporting this application is findings from a 33-month, large, multi-national, randomized, active-controlled non-inferiority trial (TBTC-S26) comparing a once-weekly, directly-observed treatment (DOT), three-month regimen of rifapentine in combination with isoniazid (3RPT/INH) to a nine-month, once-daily oral, self-administered regimen of isoniazid (9INH) alone in male and female adults and children greater than two years of age with confirmed latent tuberculosis infection (LTBI). The trial included two sub-trials: one focused on evaluating the regimen in subjects with LTBI and HIV co-infection and the second in pediatric subjects with LTBI with or without HIV infection. Extended enrollment was allowed in both sub-trials to increase the number of HIV-infected and pediatric subjects accordingly.

The TBTC-S26 trial enrolled males and non-pregnant females, ages two years or older, who were at high-risk for developing TB disease but who presented without active TB, including HIV-infected persons. High risk individuals included those household, or other close contacts of subjects with culture-confirmed TB disease who were tuberculin skin test (TST) positive within two years of trial enrollment. In addition, high risk persons included those who converted to be TST positive within the past two years, those who were HIV-seropositive, and those who were either TST positive subjects or children between two and five years of age with negative initial TST who were close contacts of a culture-confirmed TB case. Randomization occurred at the individual patient level and per household in a cluster design in which only the first eligible subject was randomized and all other household members received the same assigned treatment. The primary efficacy endpoint was the development of culture-confirmed TB disease in subjects who were 18 years of age or older, or the development of culture-confirmed or probable (clinical) TB disease in subjects less than 18 years of age, within 33 months following therapy initiation. The primary analysis was performed in a modified intent-to-treat (MITT) population including all enrolled subjects but excluding those found to be contact of drug-resistant TB disease or culture-negative source cases and young children who were considered ineligible because they did not have a positive TST on initial or repeat testing.

Results from analyses of the main TBTC-S26 trial verified the proportion of TB infections at 33-months follow-up was 0.18% (7/3986) and 0.40% (15/3745), corresponding to cumulative TB incidence rates of 0.19% and 0.43% in the 3RPT/INH and 9INH MITT groups, respectively. The difference (3RPT/INH-9INH) in cumulative TB incidence rate was -0.24, 95% CI (-0.50, 0.014). When assuming equal follow-up time up to 33-months post-enrollment (an ITT approach), the observed TB infection rate in the active control was approximately 0.15/100 person-years (PYs), which is markedly lower than the expected rate used to design the trial of 1.5/100 PYs. Despite the lower-than-expected event rate, non-inferiority of the 3RPT/INH regimen to the standard 9INH regimen was achieved based on a margin of 0.091%, which takes into account the addition of RPT to INH. Among the 22 cases of TB infection, there were two INH-resistant cases among the 9INH group and one rifampin-resistant case in the 3RPT/INH group suggesting no notable drug resistance patterns.

Due to significant imbalances between treatment groups in number of subjects enrolled as part of a cluster, and for a less-biased comparison between treatment groups, an analysis of only randomized subjects (first-enrolled) in the MITT population was performed. The TB infection rate at 33-month post-enrollment was 0.16% (5/3074) and 0.35% (10/3074), corresponding to cumulative TB incidence rates of 0.17% and 0.35% in the 3RPT/INH and 9INH MITT groups, respectively. The difference (3RPT/INH-9INH) in cumulative TB incidence rate was -0.17, 95% CI (-0.43, 0.09). These findings are commensurate with those among all enrolled in the MITT population.

The overall mortality at 33-months follow-up (safety population including all enrolled subjects who received at least one dose of treatment) was numerically, but not statistically significantly, lower (0.78%) in the 3RPT/INH group compared to the 9INH group (1.07%). Overall, safety was similar in both treatment groups with the exception of a higher incidence of hepatotoxicity in the 9INH group (a finding commensurate with prior experience with this regimen) and statistically significant incidence of hypersensitivity in the 3RPT/INH group compared to 9INH. More of the hypersensitivity events led to premature treatment discontinuation in the 3RPT/INH arm over control.

In the HIV sub-trial, there were 2/206 (0.97%) and 6/193 (3.10%) cases of TB infection at the 33-month (MITT population) follow-up resulting in a cumulative failure rate of 1.01% and 3.45% in the 3RPT/INH and 9INH groups, respectively. The difference in cumulative failure was -2.44%, 95% CI (-5.50, 0.62). Few deaths were observed in this sub-trial, specifically, there were 1/207 (0.48%) and 4/186 (2.15%) deaths in the 3RPT/INH and 9INH in (safety population). Findings of hepatotoxicity and hypersensitivity in this sub-trial were commensurate with the main trial findings.

In the pediatric sub-trial, the proportion of TB infections was 0/472 (0%) and 3/436 (0.69%) in the 3RPT/INH and 9INH groups, respectively at the 33-month follow-up (MITT population). The difference in cumulative TB infection rate was -0.78 leading to a 95% CI of (-1.66, 0.10). There were two reported deaths both occurring in the 9INH group, zero reported events of hepatotoxicity, and 7 (1.3%) events of possible hypersensitivity reported in the 3RPT/INH group compared to zero events in the 9INH group.

Findings from a published, supportive trial by Martinson *et al*. (NEJM, 2011), which compared a weekly combination treatment of RPT and INH (12-weeks total) to a daily INH regimen (6 months total) suggest that the estimated cumulative TB or death rates at three-years post-randomization were similar, and less than 10%, in both groups with no overall differences out to six years post-randomization. Subject-level data were not provided for this trial and therefore results cannot be fully verified.

The current Centers for Disease Control and Prevention (CDC) estimate of LTBI in the United States is approximately 11 million persons, or roughly 4% of the population, of which approximately 5-10% are at risk of conversion to TB infection when untreated[1]. Despite availability of treatment regimens for LTBI there remains a need for additional regimens and ideally those that have a shorter duration, are more tolerable and confer less toxicity risk. The proposed 3RPT/INH regimen has an advantage over existing regimens in that it is taken less frequently (i.e. once-weekly versus daily) and for a shorter total time of three months (as compared to 4, 6 or 9 months). One limitation of the regimen; however, is the

1. Latent Tuberculosis Infection: A Guide for Primary Health Care Providers. http://www.cdc.gov/tb/publications/ltbi/intro.htm

requirement that the regimen be administered under direct observation, which is important to reduce, or avoid, the possibility of developing drug resistance.

The TBTC-S26 trial, and accompanying HIV and pediatric sub-trials, provide sufficient evidence demonstrating that a three-month, once-weekly, DOT regimen of RPT/INH is non-inferior to a nine-month, daily, self-administered regimen of INH with no more than a 0.014% increase, and 0.5% decrease, in TB cumulative incidence at 33-months. Additionally, these data show that 3 months of RPT does contribute to the efficacy in the 3RPT/INH regimen. The shorter, less-frequent RPT/INH DOT regimen was also shown to confer a higher proportion of treatment adherence without any evidence of increased drug resistance. Finally, the overall safety of the 3RPT/INH regimen is commensurate with that of other LTBI regimens except for findings of increased hypersensitivity, which will require close monitoring.

2 INTRODUCTION

2.1 Overview

Rifapentine (RPT), trade name Priftin®, is a rifamycin antimycobacterial oral tablet originally approved in 1998 by FDA for treatment of active pulmonary tuberculosis. This review covers the supplemental New Drug Application (sNDA) submitted by Sanofi (the applicant) for an additional indication for RPT. The sought indication is for the treatment of latent TB infection caused by *Mycobacterium tuberculosis* in adults and children ≥2 years of age who are at risk of progression to TB disease (including those in close contact with an active TB patient, recent conversion to positive tuberculin skin test, HIV-infected subjects, or those with pulmonary fibrosis on radiograph). The proposed regimen for LTBI is RPT given in combination with isoniazid once weekly for 12 weeks as directly observed therapy. This sNDA was granted a priority review.

LTBI is defined as presence of a TB-positive skin or blood test, normal chest x-ray, negative sputum test, inactive TB bacteria, and no clinical signs or symptoms of infection. Active TB infection is defined as presence of TB-positive blood or skin test in addition to an abnormal chest x-ray, or positive sputum smear or culture, and presence of clinical signs or symptoms including coughing, fever or weight loss. According to a report published by the Centers for Disease Control and Prevention (http://www.cdc.gov/tb/publications/ltbi/pdf/TargetedLTBI.pdf), the estimated US prevalence of LTBI is more than 11 million people, or approximately 4% of the US population. Approximately 5-10% of untreated latent TB infected persons will develop active TB disease. Among persons with LTBI and untreated HIV infection, the lifetime risk of developing TB disease is approximately 10%.

The recommended first-line therapy for LTBI consists of self-administered daily or twice weekly INH for nine or six months. While effective, both INH regimens suffer from poor compliance rates due to the long treatment duration and the risk of hepatotoxicity. Alternative treatments consist of INH and rifampin (RIF) taken daily for three months or daily RIF taken for four months; however, this later regimen has not been formally evaluated in randomized clinical trials. Therefore, it can be argued that there is a continued need for improved regimens (e.g. shorter duration, less toxicity) to treat LTBI. RPT is a drug under consideration as it has a longer terminal half-life (4 to 5-fold longer) and lower *in vitro* maximum inhibitory concentrations against *M. tuberculosis* (approximately 4-fold) compared to RIF (refer to microbiology review for specifics on *in vitro* susceptibility).

2.1.1 Regulatory History

The development of RPT for LTBI began in the 1990s when the applicant provided CDC with RPT product for use in CDC-sponsored latent and acute TB treatment clinical trials. It was through this partnership that the primary trial, TBTC-S26 was conducted under IND 46,954. This trial was designed and conducted by CDC's Tuberculosis Trials Consortium (TBTC) without Sanofi's involvement as the trial was not originally designed to fulfill a regulatory objective.

The TBTC-S26 protocol was initially reviewed by FDA in 2001 followed by four protocol amendment reviews. The biggest concern expressed by FDA during the original protocol review was that the trial design was open-label, which could contribute to discordant rates in treatment discontinuation between the two treatment groups. Treatment duration was considerably longer in the active control arm (daily,

self-administered treatment for 9 months) compared to the experimental arm (weekly, directly-observed treatment for 3 months), which could naturally lead to discontinuation bias favoring the short duration (assuming similar tolerability profiles between the two groups). While the division's concern was noted, the CDC responded by outlining large challenges associated with performing a double-blind, double-dummy design for this trial. They further noted that the trial was designed to show effectiveness as measured by demonstration of similar rates in reduction of TB conversion and improved treatment compliance in the experimental arm and not efficacy. The subsequent four amendments modified the protocol to clarify inclusion criteria for subjects with HIV infection, lower the age limit criterion to allow for enrollment of children as young as two years of age, and modify the primary objective of equivalence to non-inferiority. This later change is discussed in detail in section 3.2.1.1 of this review. The statistical analyses plan was submitted to the IND on 9/29/10 and reviewed accordingly.

A pre-NDA meeting occurred between the applicant, the TBTC-S26 principle investigator and the Division of Anti-Infective Products (DAIP) on 9/4/12 during which DAIP agreed that the TBTC-S26 trial and published findings (no patient-level data provided) from a second, supportive trial performed solely in South Africa (Martinson *et al*., 2011) would be sufficient to support filing of the sNDA for a LTBI indication. During this meeting, DAIP recommended that prior to the sNDA submission, the applicant provide a detailed justification for the non-inferiority margin for the TBTC-S26 trial and additional sensitivity analyses of the trial to account for the large number of missing data due to losses to follow-up, death and other reasons. Both of these statistical items and implications are discussed in detail in section 3.

2.1.2 Trials Reviewed

This review will cover two randomized clinical trials (briefly summarized in Table 1); the TBTC-S26 trial (and accompanying sub-trials) and the published trial by Martinson *et al*. (2011).

Table 1. Trials Included in this Review

Trial	Design	Study Population	Follow-up	3RPT/INH	9INH/Control
TBTC-S26	MC, R, OL, AC	Adults and pediatrics (>2 yrs) with LTBI w/or w/o HIV	33 months post-randomization	ITT: 4145 MITT: 3986	ITT: 3908 MITT: 3745
HIV Sub-Trial		HIV Seropositive		ITT: 208 MITT: 206	ITT: 195 MITT: 193
Pediatric Sub-Trial		Pediatrics (2-17 yrs)		ITT: 552 MITT: 472	ITT: 506 MITT: 436
Martinson *et al.*, 2011	OL, R, AC	HIV-infected adults w/LTBI	6 years post-randomization	329	3RIF/INH: 329 Cont. INH: 164 6INH: 328

Abbreviations: MC=multi-center (US, Canada, Brazil and Spain), R=randomized, OL=open-label, AC=active-control; 3RPT/INH: 3-months (12-dose) regimen of weekly rifapentine and isoniazid via directly observed therapy (DOT); 9INH=9-month (270-dose) regimen of daily isoniazid, cont. INH=daily dosing for up to 6 years, 6INH=daily dosing for 6 months, ITT=intent-to-treat, MITT=modified ITT (all enrolled subjects meeting TB inclusion criteria)

2.2 Data Sources

Data were submitted electronically to \\CDSESUB1\evsprod\NDA021024\0016\m5\datasets.
The applicant's SAS programs used to create the primary efficacy and some secondary safety analyses are located in \\CDSESUB1\evsprod\NDA021024\0016\m5\datasets\tbtc-s26\analysis\adam\programs.

The clinical study reports for trial TBTC-S26, documentation of statistical methods (located in study-TBTC-S26a.pdf) and relevant publications covered in this review are located in \\CDSESUB1\evsprod\NDA021024\0016\m5\53-clin-stud-rep\535-rep-effic-safety-stud\latent-tuberculosis\5351-stud-rep-contr.

Results from FDA-recommended sensitivity analyses are provided in the summary-clin-efficacy-ltbi.pdf located in \\cdsesub1\evsprod\NDA021024\0016\m2

The proposed product label is located in \\CDSESUB1\evsprod\NDA021024\0016\m1\us.

The TBTC-S26 trial statistical analyses plan was provided in study-tbtc-s26a.pdf (section 16.1.9) located in \\CDSESUB1\evsprod\NDA021024\0016\m5\53-clin-stud-rep\535-rep-effic-safety-stud\latent-tuberculosis\5351-stud-rep-contr\tbtc-s26.

Two responses to information requests were included in this review (SDNs 140 and 146).

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This submission contains three primary data sets from the TBTC-S26 trial: results from the main trial, pediatric sub-trial and the HIV sub-trial. Overall, the data organization was difficult to follow since the data in the sub-trials were provided separately, yet a large number of subjects were part of both the main study and one of the sub-trials and therefore included in both data sets. Subjects only included in an extension phase of either sub-trial were not provided in the main study results, which created confusion when attempting to verify the overall numbers presented in the clinical study reports and the clinical overview document.

The TBTC-S26 trial was initiated in 2001 prior to Clinical Data Interchange Standards Consortium (CDISC) standards; therefore this submission contains three types of databases: the legacy, CDISC Analysis Data Model (ADaM) and CDISC Study Data Tabulation Model (SDTM). The SDTM was created from the legacy database (created by CDC). The SDTM-mapped data represents the raw data and was then used by the applicant to create the ADaM datasets. However, the TBTC-S26 Clinical Study Report (CSR) was written one year prior to the legacy database conversion to SDTM. To verify that the converted SDTM database would support the CSR, the applicant conducted a limited re-analysis (focused on key safety and efficacy outcomes) using the ADaM database.

Reviewer Comment: The ADaM database served as primary for purposes of this review; however, key data on subject disposition and efficacy were reviewed in both the legacy and SDTM databases. A key discrepancy was a difference of 12 subjects appearing in first-enrolled modified intent-to-treat population in the legacy ADSLCDC dataset but not in the ADaM ADSL dataset. An information request was sent to the sponsor on 10/29/14 requesting that this discrepancy be addressed. In a response from the sponsor on 10/31/14, they stated that these 12 subjects were initially enrolled as the second members in their clusters but when the first members, randomized as the index case for their cluster, were found to be ineligible for the MITT population, the first member assignment was transferred to these second enrolled patients in each clusters. Cleary this re-assignment of status violates the randomization. Therefore the ADaM ADSL will serve as the primary source to determine subject membership in the MITT population.

3.2 Evaluation of Efficacy

The primary sources of evidence supporting this application are data, findings, and conclusions from the TBTC-S26 trial (and HIV and pediatric sub-trials). A secondary source is published findings (no patient-level data provided) from the South African trial by Martinson *et al.* (2011). Each trial is separately described below.

3.2.1 TBTC-S26 Trial

3.2.1.1 Study Design and Endpoints

The TBTC-S26 trial entitled, "*A Study of the Effectiveness and Tolerability of Weekly Rifapentine/Isoniazid for Three Months Versus Daily Isoniazid for Nine Months for the Treatment of Latent Tuberculosis Infection*" was a Phase 3, open-label, multi-center, multi-national, parallel-design, trial originally designed to show equivalence and later modified for a non-inferiority objective.

The trial enrolled males and non-pregnant females, ages two years or older, including HIV-infected persons, who were at high-risk for developing active (clinical) TB disease but who presented without active TB. High risk individuals included those household, or other close contacts of subjects with culture-confirmed TB disease who were TST positive within two years of screening. In addition, high risk persons included those who converted to be TST positive within the past two years, those who were HIV-seropositive, and those who were TST positive subjects or children between two and five years of age with negative initial TST who were close contacts of a culture-confirmed TB case.

Persons excluded from the trial included those with culture-confirmed or clinical TB disease, suspected TB disease, TB resistant to INH or RIF in the source (index) case of TB disease, had a history of completing an adequate course of treatment for TB disease or latent TB and HIV-seronegative, had elevated liver enzymes, were pregnant or nursing, currently receiving or planning to receive antiretroviral therapy in the first 90 days of enrollment, and weighed less than 10 kilograms (kgs).

Primary Objective and Endpoint

The primary research objective was to compare the effectiveness of a 3-month (12-doses total) regimen of weekly RPT/INH (3RPT/INH) to the effectiveness of a 9-month (270-doses total) regimen of daily INH (9INH) among children and adult high-risk TST reactors.

The primary endpoint was defined as **development of culture-confirmed TB disease in subjects who were 18 years of age or older, or the development of culture-confirmed or probable (clinical) TB disease in subjects less than 18 years of age, within 33 months following enrollment.**

Culture-confirmed TB was determined via findings of at least one positive culture for *M. tuberculosis* obtained from any body fluid or tissue. Probable (clinical) TB was determined based on objective evidence (cough, fever, night sweats, weight loss, or hemoptysis) of TB from medical history and/or physical examination PLUS radiograph, computed tomography scan, and/or other diagnostic tests and absent a concurrent illness that could explain findings. All cases of probable (clinical) TB were reviewed by three independent reviewers at the end of the trial.

Reviewer Comment: While death is often a primary analyses event, given the low TB infection rate observed in the trial, including deaths in the primary analyses may distort the interpretation regarding risk of TB conversion in LTBI. Both the applicant and reviewer performed sensitivity analyses to include deaths (and losses to follow-up) with TB infections. Deaths were also considered in the assessment of treatment-emergent adverse events that might have resulted in death.

Treatment Arms and Dosing

3RPT/INH (experimental arm)

Subjects who were 12 years of age or older received INH 15 mg/kg (rounded to nearest 50 or 100 mg; 900 mg maximum) **once-weekly**, orally, by DOT for 12 doses (3 months).

For subjects 2-11 years of age, INH was dosed at 25 mg/kg (rounded to nearest 50 or 100 mg; 900 mg maximum) once-weekly, orally, by DOT for 12 doses (3 months).

RPT was administered **once weekly** (in combination with INH), orally, by DOT for 12 doses (3 months) with INH and dose was based on weight, as follows:

Weight (kg)	RPT Dose (mg)
10.0-14.0	300
14.1-25.0	450
25.1-32.0	600
32.1-50.0	750
>50.0	900

Completed therapy in the experimental arm was defined as having received at least 11 doses (~90%) of protocol-specific doses within a 16-week time period.

9INH (control arm)

Subjects who were 12 years of age or older received INH 5 mg/kg (rounded up to nearest 50 or 100 mg 300 mg maximum) **daily** by mouth, self-administered for 270 doses (9 months).

Subjects 2-11 years of age received INH 10-15 mg/kg (rounded up to the nearest 50 or 100 mg dose; 300 mg maximum) **daily** by mouth for a total of 270 doses (9 months).

Completed therapy in the control arm was defined as having received at least 240 doses (~90%) within 52 weeks (39 weeks optimal).

Given the risk of INH-associated peripheral neuropathy, it was recommended that subjects in both treatment arms receive pyridoxine (vitamin B6) 50 mg with each dose of INH.

Trial Assessments

Treatment Phase
Assessments occurred every 4 weeks during the treatment phase. Assessment during the treatment phase in the 3RPT/INH occurred at weeks 4, 8, and 12. Assessment during the treatment phase in the 9INH occurred at weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36.

Follow-Up Phase
Assessments occurred every 3 months up until month 21, then became every 6 months until the end of the study. Follow-up assessments in the 3RPT/INH arm occurred at months 6, 9, 12, 15, 18, 21, 27 and 33. Follow-up assessments in the 9INH arm occurred at months 12, 15, 18, 21, 27 and 33.

Follow-up visits were conducted via telephone, email or regular mail or in person. In-person visits were required for subjects who developed signs and symptoms of infections or who could not be reached via the other methods.

Reviewer Comment: Due to different treatment durations, six additional on-treatment assessments were performed in the 9INH group compared to the 3RPT/INH group, which could bias findings for on-treatment safety assessments (adverse events collected on therapy and up to 60-days following treatment completion) in favor of the 3RPT/INH group. This issue was raised by the trial DSMB who suggested that CDC collect all grade 3/4 toxicities within a year following enrollment in both groups. This recommendation does not appear to have been incorporated into the trial design. The CDC addressed this concern by amending the protocol to include a time-to-event AE analyses using time-event as a percentage of doses taken prior to the AE and number of days from enrollment to the early departure (not defined), up to 90 days. The protocol was not amended to reflect changes in AE data collection.

HIV testing was recommended, but not required, at time of enrollment and testing was offered at any time during the trial. Documentation of HIV-seropositivity required written documentation of a positive enzyme-linked immunosorbent assay and confirmatory test such as Western blot, or HIV-1 viral load ≥5000 copies/mL by reverse polymerase chain reaction or ≥2500 copies/mL by b-deoxyribonucleic acid. A CD4+ count was required at baseline for HIV-seropositive subjects.

Reviewer Comment: Since HIV testing was not required at time of enrollment, the overall number of HIV seropositive subjects enrolled in the trial is likely under-estimated and not fully indicative of the HIV-seropositive population at risk of converting to TB infection.

Treatment Blinding

Despite recommendations from DAIP to conduct the TBTC-S26 trial as a double-blind trial, treatment was open-label. The justification provided by CDC for the open-label design was that blinding would be overly complicated given the differing treatment durations and approaches (i.e. 3 months of weekly RPT/INH, DOT v. 9 months of daily INH alone, self-administered). The CDC further argued that administering daily doses of an active treatment or a placebo (i.e. a double-dummy design to maintain a double-blind) via DOT to approximately 8,000 subjects would not be logistically feasible.

Reviewer Comments:

- ***The CDC's argument against a double-blind design is flawed. Daily DOT would not be required but rather, under a double-blind, double-dummy design, each subject would receive one daily (self-administered) INH tablet or matching placebo (for subjects in the 3RPT/INH group) for nine months and a once-weekly (DOT) RPT/INH or matching placebo regimen (for subjects in the 9INH group) for a total of three months. While this design would require the production of matching placebos, it is feasible.***
- ***The different treatment durations, i.e. 3 vs. 9 months, likely contributed to the efficacy favoring the 3RPT/INH treatment arm. In fact, more subjects in the 3RPT/INH arm (84.1%) compared to the 9INH arm (71.6%) received >90% of all protocol-specified doses. It is not possible to distinguish efficacy due to TB activity of the regimen based on regimen adherence as the duration of the regimen is an inherent characteristic of the regimen itself.***

3.2.1.2 Statistical Methodologies

Randomization

Randomization was stratified according to baseline HIV status and clinical site using a blocked design (random sizes of 2, 4 or 6 subjects) by site. Two randomization tables, including 46,000 units (1-46,000) were created; one table for HIV-positive subjects and one for HIV-negative/status-unknown subjects. The allocation ratio was 1:1 to each of the two regimens in each HIV subgroup. Initially when the trial began in 2001, treatment was assigned via a telephone-based system but later changed, in 2004, to via a web-based application. The same randomization tables were used throughout the trial regardless of method of assignment.

Reviewer Comment: The applicant provided a detailed summary of how each method, i.e. telephone- and web-based randomization was performed. The methods appear to be satisfactory.

Randomization occurred at the individual patient level and per household. Per household randomization (or cluster randomization) included randomization of only the first eligible participant and all other household members received the same assigned treatment. Household members who became eligible after randomization of the first-eligible member were not randomized into the trial.

Reviewer Comments:

- ***Then trial DSMB raised concerns regarding cluster sizes of ten or larger all appearing in the arm B (groups were masked to the DSMB but this can be assumed to be 3RPT/INH) apparently due to***

investigators enrolling additional patients in a cluster once the index case is randomized to treatment (the major issue with the open-label, cluster enrollment of this trial). They recommended limiting cluster sizes to 9 or fewer, determine cluster size in advance, include only first enrolled in the primary analysis, or consider a secondary analyses including cluster-enrolled subjects while accounting for correlation. It is unclear how, or if, the CDC ultimately modified the enrollment cluster sizes; however, they did include in the protocol, plans to compare TB infection rates between groups in the first-enrolled MITT population as a secondary analyses.

- ***To account for the per-individual and per-household randomization structure, the applicant performed two set of analyses: 1) analyses of only the first member of the each household, and 2) analyses of all enrolled subjects.***

In a communication with the applicant, FDA recommended that randomization account for age (i.e. stratify by age group: ≤18 years and >18 years). The CDC responded that the sample size of subjects <18 years of age was expected to be small and therefore randomization by this variable was not performed; however, an analyses stratified by age was performed.

Randomization Inconsistencies

The applicant reported 13 randomization codes/units that were skipped in the HIV-negative/unknown table. These occurred at sites 13 through 16 and site 20 (n=1 skipped at each), site 17 (n=4), site 29 (n=2) and site 40 (n=2). For those sites with more than one skipped code, the skipped codes occurred consecutively (e.g. at site 17 the units that were skipped included 4600-4603) suggesting that the error occurred at one time rather than a repetitive error.

A study participant was enrolled at site 12; however, no randomization code/unit was used for this participant. This site used 24 randomization codes/units from the non-HIV table but had 25 enrolled participants enrolled not as members of a previously identified household. The data center staff concluded this additional participant was most likely a member of household despite the lack of verifying documentation.

During the paper-based (telephonically based) randomization process, there were some blocks at specific sites that were skipped. For example, at site 13, while the telephone-based system was in use, randomization codes 1501-1617 were assigned followed by 1747-1774 meaning that codes 1618-1746 were skipped. Once the process was changed over to the web-based platform, the system picked up the unused blocks. The applicant further notes that there were three participants (26-13-1807, 26-13-1894 and 26-13-1921) who were assigned numbers (1747, 1749 and 1750, note that 1748 was skipped) not fitting into this explanation. These three subjects were all assigned to the 9INH group (1748 had assignment 3RPT/INH).

The applicant performed a review comparing the randomization tables against treatment assignments. One participant (26-40-8419) was randomized during the HIV and pediatric extension period but was neither HIV-seropositive nor less than 18 years of age at time of enrollment. This participant completed treatment per protocol, had no AEs and did not develop TB but was omitted from the analyses.

There were 4 duplicates enrolled but not included in the applicant's 'Enrollment' dataset, and were not analyzed. The 3 duplicates affecting randomization were: 26-17-8109 a duplicate of 26-17-8108; 26-29-4292 a duplicate of 26-29-4283; 26-59-7836 a duplicate of 26-59-7837. The applicant kept the first random assignment if a duplicate assignment occurred except for the third pair, for which the second assignment was retained, 26-59-7837; in this case both units had the same treatment so there would have been no difference in treatment assignment if 26-59-7836 had been retained. The 4th duplicate (26-24-5841 a duplicate of 26-24-5846; neither was randomized) is a household member with participant 26-24-5840.

There were thirteen randomization units/codes marked as 'allocated' but for which there were no enrolled subject data.

There were 22 subjects for whom there was a change in an enrollment characteristic following enrollment. A summary follows:

- HIV status changed from unknown to HIV (+) for 10 subjects: 26-14-1969, 26-20-130526-22-2203, 26-22-3430, 26-28-7502, 26-31-5567, 26-58-0493, and 26-63-1615. Two subjects (26-58-0493 and 26-63-1615) developed TB infection (one in each treatment group). Two additional subjects were enrolled and analyzed as HIV sero-positive but subsequent documentation revealed that they were HIV sero-negative. Neither subject developed TB infection. Household status changed from not being member of a household to being members for eleven subjects: 26-13-0447, 26-15-3533, 26-20-3439, 26-20-7057, 26-23-7022, 26-24-0239, 26-26-7337, 26-26-7338, 26-29-2493, 26-29-4818, and 26-29-5523 enrollment forms were edited after enrollment, from not being in a previously randomized household, to being in the same household as a previously randomized participant.
- Site status changed for one subject after enrollment.
- Two subjects (26-20-6740 and 26-26-4034) could not be matched with the randomization tables but were included in the primary MITT analysis. Neither developed TB infection. One was assigned to the experimental treatment and one to the active control treatment.

Reviewer Comment: There is no evidence suggesting that these randomization errors/inconsistencies were biased in favor of one treatment over another. However, due to the open label design, we cannot exclude the possibility that many of these errors were due to the decisions by the investigators to have certain subjects assigned to a particular treatment group. Additionally, the complexity of the cluster randomization design, in an open-label trial where members of the cluster were potentially enrolled after knowledge of the randomized treatment assignment, may have also led to both inadvertent and deliberate errors in treatment assignment.

Analyses Populations

Intent-to-Treat (ITT): All randomized subjects including those found to be ineligible (contacts of drug-resistant TB disease or culture-negative source cases, and young children who were considered ineligible because they did not have a positive TST on initial and repeat testing) after randomization. While all follow-up time was used, subjects found to be ineligible were not followed for trial endpoints.

Modified ITT (MITT) (applicant's primary analysis population): All enrolled subjects found to be eligible for the trial. Non-eligible subjects were those subjects who were found to be contacts of drug-resistant TB disease or culture-negative source cases, and young children who were considered ineligible

because they did not have a positive TST on initial or repeat testing. To address the possible effect of clustering and provide the truest assessment of differences by treatment arms, the applicant proposed a MITT analysis of all randomized subjects found to be eligible for the trial. This population would exclude subjects other than the first person enrolled into a cluster. This is the same as the first-enrolled MITT.

Reviewer's Comment: The original study analyses plan stated that the primary analyses population would be the intent-to-treat; however, this was later changed to the MITT following input from DAIP.

Two time-based cohorts were considered in the analyses of the MITT population: 33 months after trial enrollment (the primary analyses population) and 24 months following treatment completion (a secondary analyses population).

Per-Protocol (PP): The PP population included all enrolled and eligible study subjects (MITT population) who:

1. Completed study drug within the targeted time period (11-12 doses of RPT/INH within 10 to 16 weeks or 240-270 doses of INH within 35 to 52 weeks); or
2. Developed TB disease or died while on study therapy (or during follow-up) but completed at least 75% of the expected number of doses prior to the event.

Data collected in the PP population were analyzed at 33-months post enrollment and 24-months post treatment completion.

Safety: All randomized subjects who took at least 1 dose of study drug were included in the Safety population, regardless of trial eligibility or if they were randomized individually or part of a cluster.

Reviewer Comment: The 24-month analyses excluded patients who had reached an endpoint (i.e. developed TB disease, died, or withdrew consent) during the treatment phase because they did not contribute any post-treatment follow-up data. Endpoints were considered as having occurred during the treatment phase if they occurred within 7 days from the last dose date. The reviewer considers these secondary analyses biased as they exclude patients based on a post-randomization findings. Consequently, results of the 24-month PP and MITT secondary analyses are not presented in this review. Additionally, relying on 24 month post-treatment follow-up does not allow for a comparable timeframes between the two groups from the point of randomization. The 3 month group will be assessed to month 27 from randomization while the 9 month group will be assessed to month 33 from randomization.

First-Enrolled MITT (reviewer's primary analysis population): Defined as all MITT subjects who were randomized to treatment. This population therefore excludes subjects enrolled as part of cluster but not randomized.

Sample Size Determination

TBTC-S26 was originally designed by CDC as an effectiveness trial with an objective to demonstrate equivalence of the 3RPT/INH regimen to the 9INH group. Equivalence was defined as a relative difference of +/-50% of the TB infection rate in the control arm, or, in other words, if the TB infection rate in the 9INH group was 1.5 cases per 100 PYs, then the rate in the 3RPT/INH group would have

needed to be within a range of 0.75 to 2.25 cases per 100 PYs over two years. The range was derived by taking ±50% of the expected rate of 1.5 TB cases per 100 PYs over two years in 9INH control arm. The rate of 1.5/100 was chosen based on an assumed failure rate of 30% in the 9INH control arm times an expected rate of TB without treatment among persons who were recent converters and TST-positive close contacts of persons with active TB of 5 per 100 person-years over two years. Given these assumptions and objective, the CDC calculated a sample size of 3,872 subjects per arm to have 80% power to show a two-sided equivalence with a type I error of 0.05, 15% loss to follow-up (LTF) rate. The 15% LTF rate was based on a study by Gordon *et al.* (2000).

Reviewer Comment: While not explicitly stated, it is assumed that the expected failure rate was based on estimates from two-year post treatment completion for a standard 9-month regimen, which is 33-months post-treatment initiation.

However, in May 2005, the trial DSMB noted that the pooled (at that time it ranged from 0.24% to 0.55%) primary event rate of TB cases was lower than expected (1.5 per 100 PYs in the 9INH group). This resulted in a major protocol amendment changing the margin from a relative 50% of the event rate in the 9INH group to a fixed margin of 0.75%. Additionally, the primary objective was changed from one of equivalence to one of non-inferiority, i.e. the null changing from a two-sided test of equality to a one-sided test of non-inferiority. The chosen non-inferiority margin was the same as the absolute difference of 0.75% stated under the original objective.

Justification of Trial 26 Non-Inferiority Margin

During the 9/4/12 Type 2 meeting with the applicant, DAIP requested an NI justification for rifapentine for TBTC-S26. The full justification was submitted on 2/22/2013 to IND 45138 SN/SDN 147/177 and a full statistical review of justification was conducted by Dr. Xianbin Li (review posted in DARRTs on 5/17/2013).

The following is a summary of the NI margin derivation and justification. The trial was designed assuming a TB incidence rate of 1.5 cases/1000 persons over two-years in the 9INH control arm from which the applicant choose a 'margin' of 0.75/1000 (1/2 of the expected failure rate). As requested, the applicant later reviewed published data to estimate an NI margin based on current FDA guidance to industry.

Reviewer Comment: As discussed below, the applicant's approach to the margin justification is based on showing that the full 3RPT/INH regimen is efficacious. To justify the margin, an estimate of the efficacy of the full 9INH regimen compared to no treatment would be needed. While this is of interest to the Division as well, it was also important to understand if RPT contributes to the efficacy of 3RPT/INH. To determine this, a smaller NI margin would be needed. To justify a margin for this question, it was necessary to estimate the efficacy of 9INH over three months of INH, the putative placebo (i.e., the placebo control or background regimen in a trial to test for the efficacy of 3RPT in a regime of 3RPT/INH).

The applicant presented two different approaches to calculate M1 (effect size of the active control over placebo). This method focuses on the determination of the efficacy of the regimen. The first approach used data from the IUAT Trial (Bulletin of the WHO, 1982) (at DAIP's recommendation) and compared

the 3-yr incidence between placebo and 6-month INH regimen (chosen to represent the active control because a 9-month INH regimen was not included in the study). This analysis yielded a lower bound of the 95% CI of 4.9/1000 persons. Taking 50% of M1 resulted in an estimated NI of 0.245%. The second approach was based on a Cochrane meta-analysis of 11 previously conducted placebo-controlled RCTs and yielded a pooled random effect estimate of 0.0121 and a lower bound of the 95% confidence interval of 0.0070 (summaries of the IUAT trial and Cochrane meta-analysis are Appendix A). Choosing M2to be equal to one-half of this lower bound, the applicant arrived at an NI margin of 0.0035 (0.35%). The applicant then identified the smallest trial-specific 95% confidence interval lower bound, which was 0.0034 to arrive at a margin of 0.0034 (0.34%). Therefore, depending on which approach taken, the applicant's margin to determine the efficacy of the regimen is either 0.245% or 0.34%.

In Dr. Li's review he took the analysis a necessary step further and estimated the margin by considering the 3-month INH regimen as the putative placebo in order to determine if 3RPT is contributing to the regimen. A comparison between a 3-month 900 mg weekly INH (putative placebo) and a 9-month 300 mg daily INH (active control used in TBTC-S26) was needed to estimate M1. Though the IUAT trial did not evaluate these two specific regimens (nor are there other comparative data available that compared these groups), Dr. Li considered a comparison between the 3 (12-week) and 6 (24-week) month 300 mg daily INH regimens as a conservative estimate of M1. This comparison yielded a lower bound of the 95% CI around the risk difference of 1.82/1000 persons suggesting an M2 (1/2 of M1) of 0.00091 or 0.091%.

In conclusion, the applicant estimated an NI margin of either 0.00245 (based on findings from the IUAT trial) or 0.0034 (based on a published meta-analysis of 11 RCTs) for a comparison of the two full regimens. The FDA's estimate (based on the IUAT trial) was determined in order to conclude efficacy of the 3RPT portion of the 3RPT/INH regimen and is a more conservative margin at 0.00091. **Therefore, the interpretation of the primary efficacy results will be based on the FDA's margin of 0.091%.**

Reviewer's Comment: Despite the applicant providing an NI justification of 0.245% (or 0.34%), the TBTC-S26 clinical study report references the prior 'NI margin' of 0.75%, which is based on one-half the expected incidence of 1.5 cases of TB/100 persons over 2-yrs in the 9INH control arm.

Primary Efficacy Analyses

Applicant's Analyses
The Applicant's primary efficacy analyses tested the null hypothesis (stated below) that the difference in 33-month (time from enrollment) cumulative failure rate (estimated via the Kaplan Meier method) between groups (in the MITT population) was greater than or equal to a non-inferiority margin (δ) of 0.75% letting r_a and r_b correspond to the TB event rates in the 9INH and 3RPT/INH groups, respectively. The applicant would conclude NI if the upper bound of the 95% CI around the difference in failure rates (3RPT/INH – 9INH) was less than delta. Pooled variance used to estimate confidence intervals was calculated using Greenwood's formula. The log-rank was used to compare survival between treatment arms with a two-sided type-I error of 0.05.

$$H_0 : r_b - r_a \geq \delta \quad \text{vs.} \quad H_1 : r_b - r_a < \delta$$

The analysis plan states three analyses to account for clustering. These are 1) including all subjects in the analyses without regard for cluster, 2) analysis limited to first person enrolled in the cluster, 3) statistical resampling. However, the sponsor does not provide details on plan #3 and does not report the results of this analysis in the final study report.

Reviewer's Comments: Although stated in the statistical methods plans to assess the correlation of clustering among family members these analyses do not appear to have been conducted by the sponsor. However, the applicant did report results from analyses including all enrolled (MITT) and an analyses including only randomized subjects (first-enrolled MITT).

Reviewer's Analyses
The reviewer's primary analyses considered a NI margin of 0.091% as evidence of non-inferiority of the 3RPT/INH group to the control of 9INH in the 33-month cumulative TB failure rate in the first-enrolled MITT population. The reviewer estimated cumulative failure rates and pooled variances using the same approach as that by the applicant. In addition, since follow-up time was the same in both treatment groups (i.e. 33-months post-enrolled) the reviewer calculated differences in the proportion of TB infections, TB infections and death, TB infection, death and loss to follow-up (based on subjects per treatment group) and 95% CI confidence intervals using the normal approximation to the binomial method.

Reviewer Comment: The applicant's estimation of cumulative TB failure using the Kaplan-Meier method censors subjects who were lost to follow-up, withdrew consent, or died up to 33-months post-enrollment. This censoring approach assumes that the data were non-informative, which potentially an incorrect assumption given this open-label trial design. Losses to follow-up are likely associated with treatment assignment in this open-label design and cannot be assumed missing at random. Sensitivity analyses were performed to include death and death w/lost to follow-up with TB infection events to fully account for these outcomes.

The primary efficacy analysis was performed in the first-enrolled MITT. Secondary analyses were performed in the MITT populations.

Reviewer Comment: Given imbalances in cluster sizes between treatment groups, the reviewer considers the first-enrolled MITT to be the least biased trial population to assess the primary endpoint.

Occasionally in this review, the reviewer provides estimates of rate per 100 person-years calculated as: (event count/(total number in treatment group *(33/12))*100). This approach assumes equal follow-up time for all enrolled.

Secondary and Sensitivity Analyses

Secondary analyses performed by the applicant included:
- Estimating the 33-month cumulative TB failure rates using the first-enrolled subject in a cluster in the MITT population and all subjects in the PP population using the methods described for the primary endpoint.
- Estimating the proportion of subjects completing assigned treatment with treatment completion defined as greater than or equal to 11 of 12 doses within 16 weeks in the 3RPT/INH group and greater

than or equal to 240 of 270 doses within 52 weeks in the 9INH group. The proportion of treatment completion between groups was compared using a Pearson Chi-Square, 2-sided alpha of 0.05.

- Estimating the 24-month cumulative failure rates (A24) in both the MITT and PP populations. Subjects who reached an endpoint (TB, died, withdrew consent) during the treatment phase were excluded from these analyses sets.

Reviewer Comment: The A24 secondary analyses are highly biased as they omit subjects who experienced an event while on treatment. Given that treatment duration varied between groups, any analysis based on treatment duration, rather than on duration in study, is biased and difficult to interpret. Results of this secondary data analyses are not provided in this review.

Applicant's Sensitivity Analyses: Handling of Deaths and Missing Data

The applicant performed sensitivity analyses to assess the influence of death and lost to follow-up. These analyses included:

- Comparing rates of 33-month TB and death (composite endpoint)
- Inflating TB cases in the 3RPT/INH group by treating 'excessive' deaths as failure: This conservative approach treated all deaths associated with diseases of the heart, chronic liver disease or cirrhosis and cerebrovascular diseases as failure in the 3RPT/INH group. These causes of death are considered to be associated with TB disease.
- The number of possible, but unobserved TB cases, were estimated for the portion of follow-up duration that was lost to follow-up.
- An analysis fixing the number of TB cases observed in the 9INH arm while calculating the largest possible number of TB infections required in the 3RPT/INH arm that would yield an upper bound of the 95% CI that will cross a 0.35% NI margin. Results of this sensitivity analysis are presented in this review as the reviewer does not agree with the choice of a 0.35% margin.

Reviewer's Sensitivity Analyses:

- Estimation of group cumulative failure rates when failure included TB infection, death or TB event, death and lost to follow-up at 33-months post-enrollment in the first-enrolled MITT and MITT populations

Reviewer Comment: The overall number of subjects LTF in the trial was between 10-11%. Therefore, when including LTF in the analyses when the proportions of TB and death events are relatively low, can falsely increase the overall failure estimate. Nevertheless, this sensitivity analysis was performed to assess the overall robustness of the findings via assessment of the confidence interval (results presented in section 3.2.2.4).

HIV and Pediatric Sub-Trial Analyses

The analyses of data from the HIV and pediatric sub-trials mirror those used to analyze the main trial results.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Overall, 8053 subjects were enrolled in the TBTC-S26 main trial and of these 6364 (79%) were first randomized subjects and the rest being enrolled as part of a cluster group. The total number of subjects meeting MITT eligibility criteria were 3986 (96.2%) and 3745 (95.8%) in the 3RPT/INH and 9INH groups, respectively. The most common reasons for exclusion from the MITT was the source case with INH- or RIF-resistant LTBI and TB case culture-negative for *M. tuberculosis*. The overall reasons for MITT exclusion were mostly balanced between treatment groups (Table 2).

Reviewer Comment: More subjects were excluded from the safety population in the 9INH group compared to the 3RPT/INH. Since inclusion in this population required having taken at least one dose of trial medication, this finding illustrates the major problem of open-label trials resulting in subject choosing against treatment once assigned. It also highlights a particular problem with this open-label trial whereby treatment was DOT in one arm but self-administered in the other. Naturally, proportion of subjects receiving at least one dose of treatment will be higher in the DOT group.

Additional 191 and 352 subjects were enrolled during the HIV and pediatric sub-trials extensions periods, which were performed to increase the numbers in these two sub-groups only.

Table 2. TBTC-S026 Enrollment and Disposition

Count (%)	3RPT/INH	9INH	*Total*
Main TBTC-S026 Trial			
All enrolled ITT (# randomized first person)	4145 (3174)	3908 (3190)	*8053 (6364)*
Safety^	4040 (97.5)	3759 (96.2)	*7799 (96.8)*
*Excluded for not receiving at least one treatment dose**	105	149	*254*
MITT	3986 (96.2)	3745 (95.8)	*7731 (96.0)*
Excluded from MITT (reasons below)	*159 (3.8)*	*163 (4.2)*	*322 (4.0)*
Source TB case resistant to INH or RIF	*82*	*79*	*161*
Source TB case culture-neg. for M. tuberculosis	*53*	*50*	*103*
Positive TBT not confirmed	*14*	*23*	*37*
M. tuberculosis drug susceptibility unavailable for the source TB case	*7*	*7*	*14*
TB disease at enrollment	*3*	*4*	*7*
First-Enrolled MITT	3074 (74.2)	3074 (78.7)	*6148 (76.3)*
Completed Follow-up out to 33 months	3475 (83.8)	3174 (81.2)	*6649 (82.6)*
Reasons for not reaching 33 month follow-up			
Death	*31*	*39*	*70*
Ineligible	*159*	*163*	*322*
Lost to Follow-up	*402*	*430*	*832*
Developed TB infection (primary endpoint)	*7*	*15*	*22*
Withdrew Consent	*71*	*87*	*158*
Per Protocol	3273 (79.0)	2585 (66.1)	*5858 (72.7)*
Enrolled in Extension Phases			
HIV Sub-trial	98	93	*191*
Pediatric Sub-trial	*197*	*155*	*352*
All Enrolled/Randomized including sub-trials	4440	4156	*8596*
All Safety including sub-trials	4329	4001	*8330*

Percentages are of all randomized/enrolled subjects (ITT)
^All ITT and received at least one dose of study treatment
*90 and 95 subjects in the 3RPT/INH and 9INH MITT groups respectively did not take a single dose of trial treatment. Of these subjects two subjects in the 9INH subjects developed TB infection.

Among all enrolled subjects, the mean age was 36-36.6 years, over half were males and of White race. The majority (over 80%) of subjects were enrolled in clinical sites located within the United States. Significantly more subjects were enrolled as part of cluster in the 3RPT/INH group (34.6%) compared to the 9INH group (28.9%) ($p \leq 0.0001$, Pearson Chi-Square), which is likely related to the open-design of the trial that is biased in favor of the shorter, less-frequent dosing regimen of 3RPT/INH. There were 17 cluster groups of size 10 or larger (range of size 10-31), 16 on the 3RPT/INH arm and 1 on the 9INH arm. Among these clusters of size 10-31, 220 subjects were enrolled to the 3RPT/INH treatment groups whereas only 13 subjects were enrolled as part of a cluster to the 9INH group. Again, this is evidence suggesting that the cluster enrollment was biased in favor of the 3RPT/INH treatment group. There were

no other imbalances noted between groups in the other measured baseline factors among all enrolled subjects (Table 3).

Reviewer Comment: While the overall proportion of subjects enrolled as part of cluster was less than 35% of the overall trial sample, the fact that the clustering was imbalanced toward the 3RPT/INH supports an argument that the first-enrolled MITT is the least biased population as it omits subjects enrolled as part of a cluster. This analyses population will serve as primary in this review and for purposes of labeling recommendations.

Table 3. Demographics and Characteristics (All Enrolled Population, Main Trial)

Variable	3RPT/INH (N=4145) n (%)	9INH (N=3908) n (%)
Mean age in years (sd)	36.6 (14.9)	36.0 (14.7)
≥18	3790 (91.4)	3557 (91.0)
12-17	248 (6.0)	267 (6.8)
2-11	107 (2.6)	84 (2.1)
Males	2297 (55.4)	2096 (53.6)
Race		
White	2400 (57.9)	2269 (58.1)
Black or AA	1002 (24.2)	975 (24.9)
Asian, Native Hawaiian, Pacific Islander	513 (12.4)	511 (13.1)
American Indian/Alaska Native	86 (2.1)	34 (0.9)
Other/unknown	143 (3.4)	119 (3.0)
Country		
Brazil	485 (11.7)	435 (11.1)
Canada	259 (6.2)	240 (6.1)
USA	3401 (82.0)	3233 (82.7)
Mean BMI (sd)		
Adult (≥18 years)	27.8 (6.5)	27.8 (6.8)
12-17 years	23.3 (5.2)	23.2 (5.5)
2-11 years	18.0 (4.2)	18.1 (4.1)
TST size (mm), mean (sd)	16.7 (7.5)	16.5 (7.3)
Close contract of TB Case	3012 (72.7)	2767 (70.8)
Recent TST converter	1247 (30.0)	1221 (31.2)
Fibrosis of chest X-ray	94 (2.3)	96 (2.4)
HIV Status at Enrollment#		
Seropositive	110 (2.6)	102 (2.6)
Seronegative	1816 (43.8)	1817 (46.5)
Unknown	2219 (53.5)	1989 (50.9)
History of Alcohol Abuse	1983 (47.8)	1954 (50.0)
History of Drug Use	151 (3.6)	138 (3.5)
Homeless	296 (7.1)	222 (5.7)
Current Smoker	1139 (27.5)	1058 (27.1)
Hepatitis B Virus^	99 (2.4)	98 (2.5)
Hepatitis C Virus^	42 (1.0)	60 (1.5)
Enrolled as part of a cluster	1433 (34.6)	1130 (28.9)
Number of clusters with >1 subject	462	412
Median cluster size (range)	1 (1-31)	1 (1-13)

#Status based on document written report or laboratory confirmation (not required at time of enrollment but offered to subjects). After enrollment, an additional four (4) subjects in the 3RPT/INH provided written documentation of seropositivity.
^Hepatitis B and C statuses were based on self-report and therefore the proportions are likely underestimates.
Values in parenthesis are column percentages unless otherwise specified
All enrolled include first-enrolled via randomization and cluster members

Demographic and other baseline characteristics in the MITT and first-enrolled MITT populations were similar to those summarized among the all randomized/enrolled population. Aside from an imbalance between groups in the proportion of subjects enrolled as part of a cluster group (favoring the 3INH/RPRT group), there are no apparent imbalances between treatment groups (results not shown).

3.2.1.4 Results and Conclusions

The proportion of TB infections at 33-months follow-up was 0.18% (7/3986) and 0.40% (15/3745), corresponding to cumulative TB incidence rates of 0.19% and 0.43% in the 3RPT/INH and 9INH MITT groups in the **MITT population**, respectively (Figure 1). The difference (3RPT/INH-9INH) in cumulative TB incidence rate was -0.24, 95 % CI (-0.50, 0.01) providing evidence that the 3RPT/INH treatment regimen is non-inferior, within a margin of 0.091%, to 9INH (Table 4) and that RPT contributes to the 3RPT/INH regimen. Among the 22 subjects who developed TB disease by 33-months, 4/7 (57.1%) and 8/15 (53.3%) in the 3RPT/INH and 9INH groups, respectively had completed the protocol-specified treatment (Table 4). Among the 22 confirmed cases, two were INH drug resistant TB (both in 9INH group) and one was RIF/rifabutin/pyrazinamide resistant TB (3RPT/INH group). This later case was confirmed on day 185 following the full course of 12 doses of 3RPT/INH.

Reviewer's Comment: When assuming equal follow-up time up to 33-months post-enrollment (an ITT approach), the observed TB infection rate in the active control was approximately 0.15/100 person-years (PYs) (calculated as 15/(3745 persons*33/12 years follow-up (33-months))*100), which is markedly lower than the expected rate of 1.5/100 PYs used for trial design . Therefore, we can conclude that what was observed in the TBTC-S26 trial in the active control was lower than expected. However, the rate was similar to the previous findings from the IUAT trial used to support the NI margin providing some assurance that the constancy assumption is valid. Specifically, the IUAT-reported three-year incidence rates in 6 and 12 month INH regimens were 0.26 and 0.22 per 100 PYs, respectively (data on a nine month INH regimen unavailable).

Among the **first-enrolled MITT population**, the total number of TB cases was 5 (0.16%) and 10 (0.32%) in the 3RPT/INH and 9INH groups, respectively yielding an overall difference in cumulative incidence of -0.17 and a 95% CI (-0.43, 0.09) (Figure 2). These findings are supportive of the overall finding of non-inferiority in the sponsor's primary analysis MITT population. Results of the 33-month TB failure in the PP population did not differ from those in the MITT or first-enrolled MITT (difference in cumulative TB failure of -0.19%, with a 95% CI upper bound of 0.06%).

The overall number of deaths in the safety population reported at 33-months post-enrollment was numerically higher in the 9INH group compared to 3RPT/INH (but not statistically significantly different). Specifically, there were 31 (0.77%) and 40 (1.06%) deaths leading to risk difference of -0.30, and a 95 CI of -0.73 to 0.13.

Table 4. TB Infections and Death: 33-month Post-Enrollment

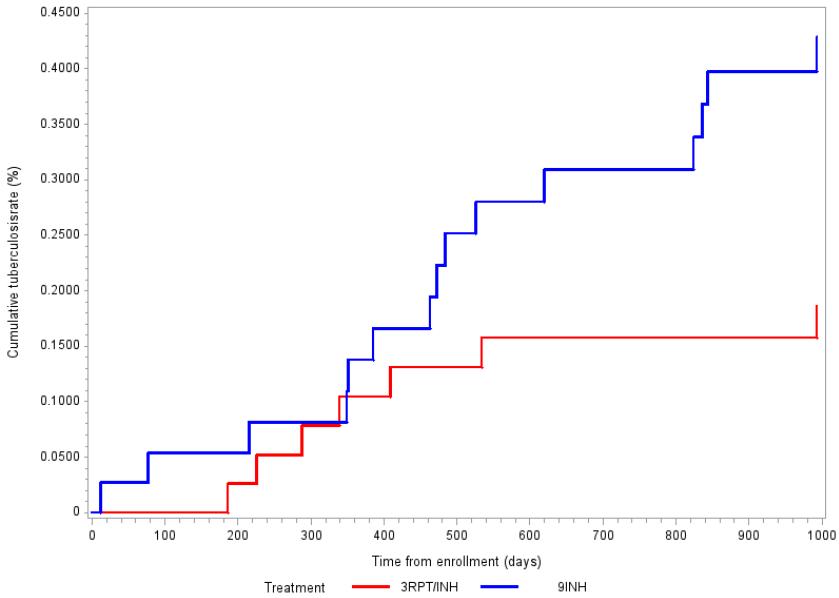
	3RPT/INH	9INH	Difference (%) (3RPT/INH-9INH), 95% CI
MITT	*n=3986*	*n=3745*	
TB Cases (%)	7 (0.18)	15 (0.40)	-0.23, (-0.48, 0.02)
Cumulative TB Rate (%)^	0.19	0.43	-0.24, (-0.50, 0.01)
Death (%)	31 (0.78)	40 (1.07)	-0.290 (-0.72, 0.14)
MITT-First Enrolled	*n=3074*	*n=3074*	
TB Cases (%)	5 (0.16)	10 (0.32)	-0.16, (-0.42, 0.01)
Cumulative TB Rate (%)^	0.17	0.35	-0.17, (-0.43, 0.09)
Death	22 (0.72)	35 (1.14)	-0.91 (-0.91, 0.06)
Safety	*n=4040*	*n=3759*	
Death	31 (0.77)	40 (1.06)	-0.30 (-0.73, 0.13)

^95% confidence interval in difference (3RPT/INH-9INH) in cumulative failure rates calculated using Greenwood's Formula for variance (pooled)
MITT-First Enrolled analyses considers events only among the randomized (excludes those enrolled as part of a cluster) subjects
The cumulative TB rate sum of product limit estimates was calculated using the Kaplan-Meier method

Reviewer's Comments:

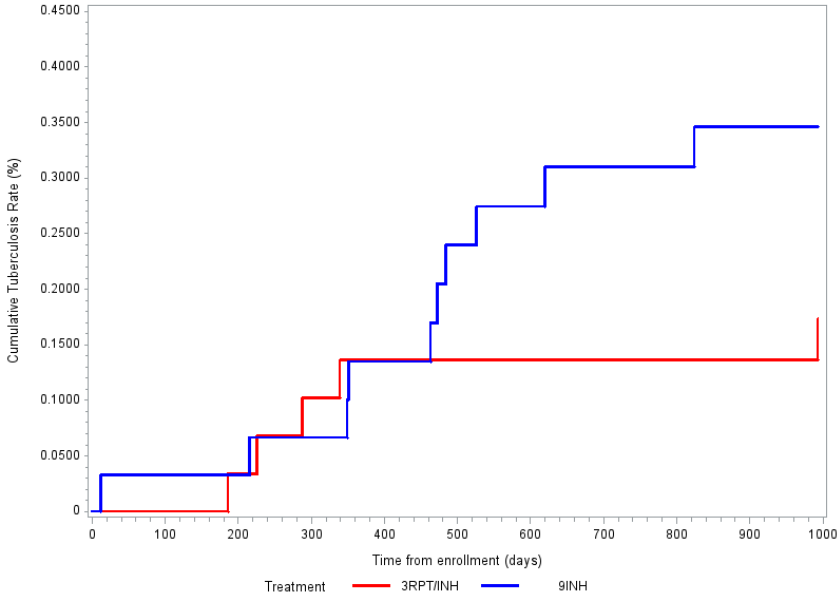
- ***Since the total events were 7 and 15 in the MITT and 5 and 10 in the first-enrolled MITT, 3RPT/INH and 9INH groups, respectively, this suggests that there were 2 and 5 events among subjects enrolled as part of a cluster. An examination of these seven TB cases revealed that none occurred among members of the same cluster/household (using site as a proxy for household as no household variable was given).***
- ***The applicant's analysis of TB infection in the first-enrolled MITT population were based on n=3082 and n=3078 in the 3RPT/INH and 9INH treatment groups, respectively. These counts were obtained from the ADSLCDC legacy dataset. However, the total number of subjects per group is reported as 3074 in the applicant's disposition summary tables and verified in all the ADaM datasets, including the ADSL. The applicant reported that the 12 subjects listed among the first enrolled MITT in the ADSLCDC legacy dataset were actually the second enrolled member of each cluster and the first member assignment was transferred to these second enrolled patients in each of these clusters. We disagree with this transfer of first member assignment. The ADaM ADSL dataset correctly report the first enrolled member and are based on n=3074/group, which represents the randomized MITT subjects. Despite this difference between the two analyses (including these 12 subjects or excluding them), the applicant's results in the first-enrolled MITT are commensurate with the reviewer's results presented above.***

Figure 1.Cumulative TB Infection Rates (%) (33-months post-enrollment, MITT)



Cumulative TB infection rates in MITT population (n=3986 3RPT/INH, n=3745 9INH) estimated via the Kaplan Meier method, log-rank test p-value=0.062, total events: n=7 3RPT/INH, n=15 9INH

Figure 2. Cumulative TB Infection Rates (%) (33-months post-enrollment, first-enrolled MITT)



Cumulative TB infection rates in the first-enrolled MITT (n=3074/group) estimated via the Kaplan Meier method, log-rank test p-value=0.1931; total events: n=5 3RPT/INH, n=10 9INH groups

3.2.1.5 Sensitivity Analyses

- **Composite endpoint of TB or death at 33-month post-enrollment (MITT population)**

There were 38 (0.95%) subjects on 3RPT/INH and 54 (1.44%) subjects on 9INH who developed TB infection, or died, during the 33-month follow-up period in the MITT population (MITT chosen over safety to exclude subject without confirmed LTBI at enrollment), difference of -0.49%, 95% CI (-0.98, 0.00), p-value 0.048. The cumulative incidence failure rates in the 3RPT/INH and 9INH groups, respectively was 1.01% and 1.54%, difference -0.49%, 95% CI (-1.01, 0.03). This finding is consistent with results from the primary analyses of TB infections only.

Reviewer's Comment: The applicant's results of this sensitivity analyses differ slightly (i.e. difference in cumulative incidence failure (MITT) of -0.54% with a 97.5% upper bound of -0.01%. The reviewer cannot verify these values; however, the overall interpretation does not change. Also, the applicant states that their derived upper bound falls below a margin of 0.35% (the applicant's revised margin). Since the NI margin was derived based on TB infections and not TB infection including death, a comparison against the TB infection margin is inappropriate.

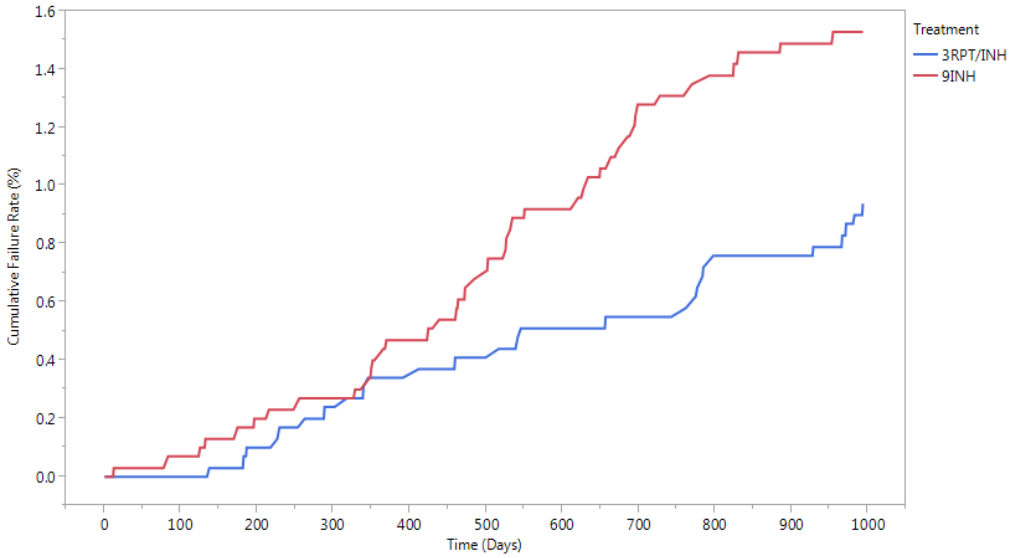
- Reviewer Sensitivity Analyses of TB, Death or LTF at 33-month post-enrollment (first-enrolled MITT and MITT)

Results of the sensitivity analyses presented in Table 5 below show that the differences in cumulative failure rate and proportion of events consistently favored the 3RPT/INH group. When including death events along with TB infections (first-enrolled MITT and MITT), the 95% CIs around differences in cumulative failures and proportions exclude zero suggesting a statistically significantly lower risk (or rate) or failure in the 3RPT/INH group compared to the 9INH group. Cumulative failure plots of TB or death in the first-enrolled MITT population are illustrated in Figure 3. Failure plots in the MITT are similar but not provided. The CIs for the other comparisons also trend below zero and are therefore supportive of the efficacy of RPT in the regimen of 3RPT/INH.

Table 5. Reviewer Sensitivity Analyses of TB, Death and LTF (33-months)

	3RPT/INH	9INH	Diff (%) (3RPT/INH-9INH) 95% CI
MITT	*n=3986*	*n=3745*	
TB/Death Events (%)	38 (1.0)	54 (1.4)	-0.5 (-1.0, 0.0)
Cumulative Failure Rate (%)	1.0	1.5	-0.5 (-1.0, 0.0)
TB/Death/LTF Events (%)	440 (11.0)	484 (12.9)	-1.9 (-3.3, -0.4)
Cumulative Failure Rate (%)	11.2	13.2	-2.0 (-3.4, -0.5)
MITT-First Enrolled	*n=3074*	*n=3074*	
TB/Death Events (%)	27 (0.9)	44 (1.4)	-0.6 (-1.1, -0.0)
Cumulative Failure Rate (%)	0.9	1.5	-0.6 (-1.2, -0.0)
TB/Death/LTF Events (%)	347 (11.3)	401 (13.0)	-1.7 (-3.4, -0.1)
Cumulative Failure Rate (%)	11.5	13.3	-1.8 (-3.5, -0.2)

Figure 3. Cumulative TB or Death Incidence Rate (%) (33-months post-enrollment, first-enrolled MITT)



Cumulative failure rate (%), first-enrolled MITT by treatment group for TB and death events, 33 months post-enrollment

- **Inflating TB cases in the 3RPT/INH arm by 'excessive' deaths (applicant's analyses)**

This sensitivity analyses sought to intentionally 'inflate' the number of TB cases in the 3RPT/INH group by including deaths associated with diseases of the heart, chronic liver disease or cirrhosis, and cerebrovascular diseases ICD9 categories (Table 6) for which there were more in 3RPT/INH group compared to the 9INH. Specifically, there were 4, 2, and 3 more deaths in these categories in the 3RPT/INH group compared to 9INH. In this analysis, these deaths were considered to have been caused by TB. When including these, the overall count of TB events becomes in the 3RPT/INH group increases from 7 to 15 thus equaling the overall number of TB events in the 9INH group.

Reviewer's Comment: While this sensitivity analysis is highly conservative favoring the control group results do not change the overall findings from the primary analyses.

Table 6. ICD9 Category for Deaths Occurring up to 33-Months Post-Enrollment (Safety)

ICD9 Category for Deaths	3RPT/INH (n=4040) n (%)*	9INH (n=3759) n (%)*
Total Deaths	**31 (0.78)**	**40 (1.06)**
AIDS	1 (0.0)	1 (2.6)
Cerebrovascular disease	4 (12.9)	1 (2.6)
Chronic liver dx/cirrhosis	4 (12.9)	2 (5.1)
Chronic lower respiratory disease	0 (0)	1 (2.6)
Chronic pancreatitis	0 (0)	1 (2.6)
Diabetes Mellitus	0 (0)	1 (2.6)
Disease of heart	8 (25.8)	4 (0.1)
Hypertension (w/ or w/o renal disease)	1 (3.2)	2 (5.1)
Intentional injuries	1 (3.2)	6 (15.4)
Malignant neoplasm	8 (25.8)	15 (37.5)
Septicemia	1 (0.0)	1 (2.6)
Unintentional injury	3 (7.7)	3 (9.7)
Unknown	0 (0)	1 (2.6)

*The denominator for the specific categories is the overall death count in the treatment group

- **Estimating potential TB cases from subjects lost to follow-up (applicant's analyses)**

The applicant provided results from three sensitivity analyses conducted to estimate the number of TB infections missed among subjects who were lost to follow-up. A total of 990 subjects (473 in the 3RPT/INH and 517 in the 9INH groups) in the MITT population either withdrew consent (n=158) or were LTF (n=832). The first method assumed a constant TB infection rate for all subjects throughout the 33-month observation period. The second method assumed that the hazard of TB infection varied over the 33-month period and that all subjects shared the same survival function. The third method considered that the missing subjects might differ from those who completed the trial in terms of risk of TB infection. Therefore, potential missed infections were estimated using the hazard assumption from method 2 but within four specific strata (current smoking (yes/no) and treatment arm). Smoking is an established factor positively associated with conversion from latent to active TB infection. The following table presents the estimated number of missing TB infections (standard error) from the three sensitivity analyses.

Table 7. Sensitivity Analyses of Missing Data (TBTC-S26)

	3RPT/INH	9INH
Subjects LTF or Withdrew Consent (33 months)	*473*	*517*
Estimated Mean Missed TB Infections (SD)		
Method 1 (constant hazard)	0.43 (0.65)	1.03 (1.02)
Method 2 (time-varying hazard)	0.47 (0.69)	1.17 (1.08)
Method 3 (strata-based, time varying hazard)		
Current Smoker	0.47 (0.68)	0.81 (0.89)
Non-Smoker	0.07 (0.51)	0.42 (0.81)

Reviewer's Comment: These sensitivity analyses consistently estimate a number of potential missing cases less than 0.5 with a standard error less than 1.0 in the 3RPT/INH group. The applicant concluded that at most 4 TB infections might have been missed among subjects lost to follow-up/withdrew consent in the 3RPT/INH group. The statistical reviewer finds these sensitivity analyses and the overall conclusions reasonable.

Analysis of Treatment Completion

The proportion of subjects in the MITT population who completed treatment, defined as receiving 11 or 12 doses taken in the 3RPT/INH group and between 240-270 doses in the 9INH group was 84.1% (3354/3986) and 71.6% (2683/3745) in the 3RPT/INH and 9INH groups, respectively (p-value <0.0001).

Reviewer Comments:

- ***These findings are as expected given the open-label trial design and fact that treatment was less frequent, DOT, and for a short overall duration in the 3RPT/INH group. In addition, by design, treatment given via DOT is intended to increase treatment compliance.***
- ***The proportions differ slightly (82.1% and 69.0% in the 3RPT/INH and 9INH groups, respectively) when using the completed treatment variable (unclear how this variable was derived) in the legacy ADSLCDC dataset. The overall conclusions regarding treatment completion are similar regardless of variable used.***

3.2.2 Martinson *et al.* (2011)

The following is a brief summary of the published study by Martinson *et al*. (2011) that was submitted as a supportive trial only. Subject-level data were not provided for this study therefore this short summary is solely based on what was provided in the publication and supporting documents. While not included in the applicant's submission, the journal website provides supplementary information specific to this trial, which includes the trial protocol, minutes from the data and safety monitoring board and analyses of time to stopping assigned treatment. These documents were reviewed for completeness.

Trial Citation: Martinson NA *et al*. New Regimens to Prevent Tuberculosis in Adults with HIV Infection. *NEJM*. 2011; 365: 11-20.

3.2.2.1 Study Design and Endpoints

The trial by Martinson *et al*. (2011) was a single center, open-label, randomized, parallel-design trial with an overall purpose to evaluate the use of a 12-week course of rifapentine given weekly or rifampin given twice weekly, both with isoniazid, isoniazid daily for up to the study duration (originally 48 months but later extended to six years) to a control regimen of isoniazid daily for six months in HIV-infected subjects not routinely receiving antiretroviral therapy and who had latent TB. The trial was not designed to compare any of the three experimental regimens to one another but rather to answer two key questions: 1) Is a longer course of INH more effective than a six-month course? and 2) Are there alternative short-course regimens that might be equally efficacious but promote better adherence?

The trial was the joint effort of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, Johns Hopkins University Center for TB Research and the University of the Witwatersrand (Johannesburg, South Africa).

This trial began in September 2002 and was conducted in Soweto-a community in South Africa which has a known high prevalence of HIV and latent TB co-infection. Latent TB infection was based on a finding of an induration diameter of 5 mm or larger in response to the tuberculin skin test. Subjects were at least 18 years of age at time of screening, not pregnant or breast feeding and did not have active TB. Active TB was ruled-out via review of a patient's symptoms, chest radiography and sputum culture-if indicated. Receipt of TB therapy for more than two months, a CD4 cell count <200 per mm3 were criteria for exclusion.

Subjects were randomized in a 2:2:2:1 fashion to one of the following regimens:

- Rifapentine (RPT) 900 mg plus INH 900 mg once weekly x 12 weeks (RPT-INH), directly-observed therapy (DOT)
- Rifampin (RIF) 600 mg plus isoniazid 900 mg twice weekly for 12 weeks (RIF-INH), DOT
- INH 300 mg daily for the trial duration of up to six years (continuous INH)
- INH 300 mg daily for six months (6-month isoniazid) (INH-6; control regimen)

All subjects received pyridoxine 25 mg (vitamin B_6) with each dose of trial medication. Co-administration with pyridoxine is felt to reduce INH-related peripheral neuropathy and other disorders of the nervous system associated with INH.

Trial visits occurred as follows:

- RPT-INH: Once weekly for the first six months, then again three months after completing therapy then every six months thereafter
- RIF-INH: Twice weekly for the first six months, then again three months after completing therapy then every six months thereafter
- Both INH groups: every two weeks for the first six months and monthly thereafter for the continuous INH group.

Subjects completing assigned treatment or who had prematurely discontinued treatment were assessed every six months until the end of the trial. During trial visits, TB symptoms were assessed via a sputum smear, mycobacterial culture, and chest x-ray. To assess liver toxicity, alanine and aspartate aminotransferase levels were measured in all subjects at one, two and six months and every six months thereafter.

This trial was monitored by the NIAID Therapeutic Trials data safety and monitoring board.

Primary Efficacy Endpoint

The primary endpoint was tuberculosis-free survival at end of study where TB-free was defined as a patient without confirmed, probably or possible TB. TB was defined as confirmed (clinical signs and symptoms along with positive culture for *Mycobacterium tuberculosis* from any site), probable (clinical

signs and symptoms with acid-fast bacilli in a sputum smear or caseous necrosis (cell death in which the tissue presents with a cheese-like appearance) in a tissue-biopsy specimen or possible (clinical signs and symptoms without microbiologic or histologic evidence but with clinical response to anti-TB therapy). Endpoints were adjudicated via an independent review committee. The trial was intended to follow subjects for up to 72 months after enrollment.

When possible, death certificates and clinical records were obtained for subjects who were lost-to-follow-up.

3.2.2.2 Statistical Methodologies

The trial was designed to demonstrate superiority of the three test regimens over the standard INH-6 (control) in preventing TB infections. Trial assumptions included a 6% annual risk of TB in TBT-positive subjects in the six-month isoniazid group and an expected reduction in TB incidence by 50% (i.e. reduction from 6% to 3% in annual incidence) in both the RIF-INH and RPT-INH regimens. In addition, it was assumed that the continuous INH regimen would reduce the annual incidence by 82% (to 1.1%) per year compared to control. Given these assumptions, the authors' estimated that within a minimum of three years follow-up per randomized subject, a total of 124 TB cases would be observed among the 1148 enrolled subjects with a 5% alpha and 90% power to detect a difference. No adjustments for the multiple comparisons are accounted for in this sample size estimate, or in the analyses except to account for an interim analysis discussed below.

The primary analyses consisted of a time to event analyses using the log rank test in the intent-to-treat population (all randomized subjects). The trial included one formal interim analyses of efficacy and used the O'Brien-Fleming alpha spending function to adjust the type I-error. This analysis was performed with an alpha of 0.006 (two sided) for each of three pairwise comparisons (6 month isoniazid comparator) when the number of accrued TB cases reached 51.

Over concerns expressed by DSMB that subjects might die of TB before diagnosis, the follow-up period was extended from two to six years and the primary endpoint was changed to include death along with TB. Following these changes, a second interim analysis was performed when there were 115 deaths or TB infections. This analysis used an alpha of 0.02.

The final analyses of TB-free survival used an alpha of 0.04.

A secondary analyses of TB-free survival was performed in a subset of subjects (as-treated) defined as subjects who received more than two months of treatment and who did not have TB within the first three months following randomization.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient recruitment began in 2002 and ended in 2005 resulting in 1150 randomized subjects (n=329 RPT-INH, n=329 RIF-INH, n=328 INH 6 months and n=164 INH ≤ 6 years) out of a total of 1528 screened. The median age at time of randomization was 30 years, over 80% were female and 99-100% Black race.

At the end of the six years follow-up, the authors report that 77.3% of all randomized subjects had been seen in the previous 6 months or had a known date of death. The reported median follow-up time was 4.0, 4.1, 3.9, and 3.9 years in the RPT-INH, RIF-INH, continuous-INH, and 6-month INH groups, respectively.

The authors report that 95.7%, 94.8%, and 83.8% of subjects in the RRT-INH, RIF-INH and INH-6 reported taking or were observed taking the protocol-specific therapy. In the continuous INH group, the authors report that 60.4% of subjects received daily INH for more than three years and 43.3% for more than four years. The median duration in the continuous group was 3.3 years. The leading reasons for early treatment discontinuation were pregnancy occurring in 34 subjects, initiation of active antiretroviral therapy in 27 subjects (all in the continuous INH group) and withdraw from the trial in 14 subjects.

3.2.2.4 Results and Conclusions

The overall proportion of TB at the 72-month follow-up was 7.3%, 7.3%, 4.9% and 6.7% in the RPT-INH, RIF-INH, continuous INH and INH-6 groups, respectively. The TB cases that were culture-confirmed were 21/24, 18/24, 5/8 and 18/22 in the RPT-INH, RIF-INH, continuous INH and INH-6 groups, respectively. Overall there were no differences noted in the proportion or rate (per 100 person-years) of TB. Similarly, overall proportions and incidence rates of death and TB or death alone did not differ among groups.

Table 8. Summary of Results from Martinson *et al.* (NEJM, 2011)

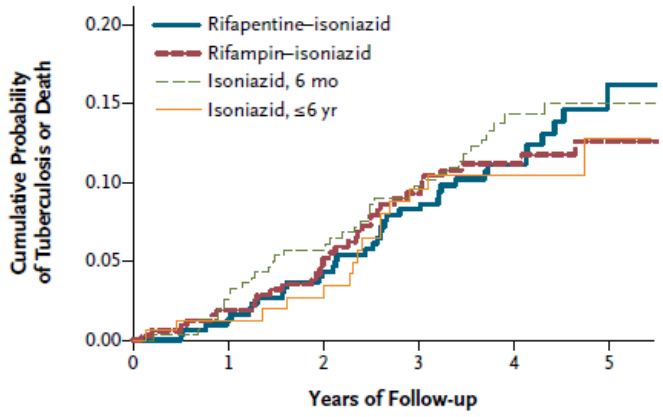
Endpoint	RPT-INH (n=329)	RIF-INH (n=329)	Continuous INH (n=164)	INH-6 mo. (n=328)
TB				
No. of Cases (%)	24 (7.3)	24 (7.3)	8 (4.9)	22 (6.7)
PY of Follow-up	1187.5	1219.7	561.0	1143.9
Incidence/100 PY	2.0	2.0	1.4	1.9
IRR (95% CI)	1.05 (0.56, 1.97)	1.02 (0.55, 1.91)	0.74 (0.29, 1.73)	Reference 1.0
P-value	*0.87*	*0.94*	*0.48*	
Death				
No. of Cases	17 (5.2)	16 (4.9)	8 (4.9)	25 (7.6)
PY of follow-up	1223.6	1269.8	574.2	1180.0
Incidence/100 PY	1.4	1.3	1.4	2.1
IRR (95% CI)	0.66 (0.33, 1.26)	0.59 (0.30, 1.16)	0.66 (0.26, 1.50)	Reference 1.0
P-value	*0.18*	*0.10*	*0.31*	
Death or TB				
No. of Cases	37 (11.2)	35 (10.6)	15 (9.1)	41 (12.5)
PY of Follow-up	1187.5	1219.7	561.0	1143.9
Incidence/100 PY	3.1	2.9	2.7	3.6
IRR (95% CI)	0.87 (0.54, 1.39)	0.80 (0.50, 1.29)	0.75 (0.38, 1.38)	Reference 1.0
P-value	*0.54*	*0.34*	*0.34*	

IRR=incidence rate ratio, 6-year follow-up time

The results in the primary time-to-event analyses are shown below in Figure 4 (duplicate of Figure 2 from the Martinson *et al*. (2011)). There were no statistically significant differences in time to TB or death in any of three pair-wise comparisons vs. the control group (INH-6 months) using the log-rank test.

Reviewer Comment: Based on visual extrapolation from the figure below, the approximate cumulative incidence of TB or death at 3 years follow-up was less than 10% in both the RPT-INH and INH-6 groups. These estimates are higher than those estimated at 33-months follow-up in the TBTC-S26 trial; however, this is somewhat expected given that the LTBI population in this trial was co-infected with HIV. The relative differences between the RPT-INH and INH-6 regimens are commensurate to those observed in the TBTC-S26 trial.

Figure 4. Cumulative Failure Rates of Death and TB (Martinson *et al*., 2000)



No. at Risk

Rifapentine–isoniazid	326	299	275	249	160	52
Rifampin–isoniazid	327	301	284	252	162	56
Isoniazid, 6 mo	327	289	260	238	145	49
Isoniazid, ≤6 yr	164	144	131	109	73	26

Figure 2. **Kaplan–Meier Estimates of the Risk of Tuberculosis or Death in the Intention-to-Treat Population, According to Treatment Group.**
The four treatment regimens were rifapentine and isoniazid weekly for 12 weeks, rifampin and isoniazid twice a week for 12 weeks, isoniazid daily for up to 6 years (continuous regimen), and isoniazid daily for 6 months (control regimen).

Reviewer Comments

1. ***The sample size was based on an expected total number of TB cases up to 48 months follow-up of 124. As observed in this trial, at the end of the trial there were only 78 cases (1.9 cases per 100 PYs) of TB observed. Despite this lower-than-expected number, cases were similarly distributed across the four treatment arms suggestive of no qualitative differences among the groups. The authors address the lower than expected rate in the control group by suggesting that the treatments used in this trial performed better than those used in prior trials in African populations. This indirect comparison cannot be verified in this review.***

2. ***The lower-than-expected number of TB cases was noted by the trial DSMB and consequently the trial primary endpoint was changed to include death among TB cases to account for potential***

deaths due to undiagnosed TB. Despite this change, the four treatment arms did not differ with respect to annual incidence of death or TB.

3. ***Overall, this publication is of good quality as it includes sufficient details on the patient disposition, sample size derivation and primary analyses. In addition, the choice of primary endpoint of TB infection or death is a preferred endpoint particularly for a trial with this long duration of follow-up.***

4. ***Despite the large sample size and long follow-up, this trial was performed at a single site in South Africa among mostly black, female, HIV-infected subjects not receiving antiretroviral therapy. Therefore, the overall generalizability of these findings to a US-based population of subjects co-infected with HIV and latent TB is somewhat limited.***

3.3 Evaluation of Safety

The following safety analyses are based solely on data from the TBTC-S26 trial with a specific focus on two treatment-emergent adverse events (TEAEs) of interest*:* ***hepatotoxicity and hypersensitivity reactions*****.** The former is a known toxicity associated with isoniazid treatment but of focus here given the concern of a potential increased risk when adding isoniazid to rifapentine. Hypersensitivity was found to occur more commonly than expected in the 3RPT/INH group and therefore assessed in greater detail by both the applicant and division review team. In general, the safety profiles of isoniazid and rifapentine (or rifampin) are well understood so this safety assessment will not cover the already well-described safety patterns.

Hepatotoxicity

The protocol-definition of hepatotoxicity was an aspartate aminotransferase (AST) greater than or equal to 3 times the upper-limit of normal (ULN) in the presence of specific signs or symptoms of hepatitis or an AST greater than 5 times the ULN regardless of signs/symptoms of hepatitis or an event deemed by the treating clinician investigator as hepatotoxicity. Signs and symptoms associated with hepatotoxicity included yellow skin or eyes (jaundice), nausea, vomiting, loss of appetite (anorexia), fatigue, weakness, abdominal discomfort/pain over liver, dark urine, pale stools, and itchiness.

It is well-understood that hepatotoxicity is a common treatment-related adverse event associated with INH, RIF and PZA anti-tuberculosis treatments. The severity of this toxicity can range from asymptomatic elevations in serum transaminases to hepatic failure leading to liver transplantation or even death. It is less understood how this risk increases when INH is given in combination with another anti-tuberculosis agent such as RPT. Therefore, a specific assessment of reported hepatotoxicity events was performed by the reviewer to verify the events reported in the applicant's results. Overall, there were 25/4040 (0.62%) and 111/3759 (2.95%) (P-value <0.001, Pearson Chi-Square) reported TEAEs of hepatotoxicity, which were defined as an event occurring from time of treatment initiation up through 60-day following the last dose received in the 3RPT/INH and 9INH groups, respectively (safety population). The incidence of hepatotoxicity by gender did not suggest a gender by treatment interaction (56% (14/15) and 46.8% (52/111) events in male subjects in the 3RPT/INH and 9INH groups, respectively). There were

15 events of hepatotoxicity categorized as a severity level grade 4 (events which led to severe limitation in activity, medical intervention or hospitalization) of which 12 were occurred in the 9INH group and 3 in the 3RPT/INH group. All other reported events of hepatotoxicity were considered either grade 1 or grade 2. Hepatotoxicity events resulted in hospitalization in three patients in the 9INH treatment arm (none in the 3RPT/INH treatment arm). No patients died or required a liver transplant due to hepatotoxicity during the trial.

Reviewer's Comment: The applicant reports a total of 113 (3.0%) TEAEs of hepatotoxicity in the 9INH group and 24 (0.6%) in the 3RPT/INH group. These numbers vary slightly from the reviewer's overall numbers, which were determined by analyzing the applicant's ADaM ADAE dataset using the AE lower-level term. Despite the small differences, the overall conclusion is the same, which is that there does not appear to be an increased risk of hepatotoxicity in the 3RPT/INH regimen compared to a longer dosing regimen of 9INH alone. Refer to the clinical review by Dr. Hala Shamsuddin for a more-detailed review of the liver-related TEAEs.

Hypersensitivity

A second area of concern explored in the main TBTC-S26 trial data was of TEAEs of hypersensitivity (HS), which was notably more incident in the 3RPT/INH group compared to the 9INH group. The rationale for systematically evaluating hypersensitivity events was knowledge that rifampin is associated with development of hypersensitivity syndrome, though the incidence is not well described. Therefore, HS TEASs were evaluated by the applicant using specific Medical Dictionary for Regulatory Activities (MedDRA) terms resulted in a finding of 161 (4.0%) and 18 (0.5%) events in the 3RPT/INH and 9INH groups, respectively. In a second analyses of ***possible*** treatment-related HS events based on a pre-specific set of signs and symptoms the applicant identified 152 (3.8%) and 17 (0.5%) events in the 3RPT/INH and 9INH groups, respectively. Regardless of definition used, the proportion of events was statistically significant higher ($p<0.001$) in the 3RPT/INH group compared to the 9INH group. Among the 152 event of possible HS in the 3RPT/INH group, 76% resulted in permanent drug discontinuation and 55% were considered Grade 3 or 4 and none resulted in death.

3.4 Benefit-Risk Assessment

The purpose of treating patients with LTBI is to prevent, or reduce, the overall risk of active TB infection, which is clinically more difficult to manage due to the complicated treatment regimen with associated toxicities and resistance concerns. Available LTBI treatments exist; however, these regimens are generally required to be taken for 4-9 months (depending on the regimen) and often require daily administration thus leading to the potential for poor compliance and a potential for increased risk of drug resistance. The 3RPT/INH combination regimen is shorter in duration and required to be taken only once-weekly but under direct observation (this later point is a limitation). Findings from the TBTC-S26 trial show that the overall risk of active TB infection was lower and commensurate to that of the standard 9INH regimen with no added increased risk of death. In addition, treatment compliance was more favorable in the 3RPT/INH regimen compared to the 9INH regimen likely due to the shorter duration of treatment and requirement that the treatment is given under direct observation. Safety concerns of possible hypersensitivity reactions, some of higher severity levels (grade 3 or higher) and leading to permanent drug discontinuation are notable for the 3RPT/INH regimen. Considering the inverse of the

risk difference, the reviewer estimates that for every 30 subjects treated with 3RPT/INH, one will experience a possible hypersensitivity event compared to zero treated with 9INH. Conversely, incidence of hepatotoxicity was lower in this regimen compared to the 9INH regimen, which is a positive finding given that hepatotoxicity is a known toxicity associated with many of the existing LTBI treatments. In terms of number needed to harm, the reviewer estimates that for every 42 subjects treated with 9INH, one will experience an event of hepatotoxicity compared to zero treated with 3RPT/INH. Therefore, overall efficacy, treatment compliance and lower hepatotoxicity risk favor the 3RPT/INH regimen (assuming similarity between regimens for all other known safety toxicities) despite the increase risk of hypersensitive and requirement for directly-observed administration of the regimen.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

TBTC-S26

Subgroup analyses of TB cases at the 33-month follow-up in the MITT population by age category (2-11, 12-17 and ≥18 years of age), gender, race and country are presented below in Table 9. The majority of TB events occurred among subjects who were 18 years of age or older, which is expected given that this was the largest age category in the trial. Compared to female subjects, slightly more male subjects met the primary endpoint; however there was no evidence of an interaction by assigned treatment. The majority of events occurred among subjects of White or Black race with no suggestion of a treatment-related imbalance. Finally, the majority of events occurred among subjects enrolled at US sites, which is expected since the majority of sites were in the US.

Table 9. Analysis by Age Group, Gender and Country (MITT Population)

Subgroup	3RPT/INH (N=3986) n (%)	9INH (N=3745) n (%)
Age	*TB Cases/n (%)*	*TB Cases/n (%)*
≥18 years	7/3664 (0.19)	12/3430 (0.35)
12-17 years	0/235	1/254 (0.39)
2-11 years	0/87	2/61 (3.28)
Female*	2/1775 (0.11)	6/1741 (0.34)
Male	5/2210 (0.23)	9/2004 (0.45)
Country		
Brazil	0/444	3/404 (0.74)
US/Canada	7/3542 (0.20)	12/3341 (0.36)
Race		
White	4/2296 (0.17)	8/2160 (0.37)
Black/African American	3/978 (0.31)	5/947 (0.53)
Other	0/124	1/107 (0.93)
American Indian/Alaskan Native	0/84	1/33 (3.0)
Asian/Hawaiian/Pacific Islander Native	0/494	0/490
Unknown	0/10	0/8

**Gender missing for one patient (USUBJID TBTC026/2029) in the 3RPT/INH group*

4.2 Other Special/Subgroup Populations

4.2.1 TBTC-S26 HIV Sub-Trial

HIV Sub-trial

The original protocol allowed for enrollment of HIV-seropositive subjects; however, due to low enrollment during the main trial period, the protocol was amended in 2007 to extend enrollment beyond the date when the target sample size (for the main TBTC-S26 trial) was reached to recruit additional HIV-infected subjects only. The second enrollment period was continued to the end of 2010 (main study enrollment ended in February 2008, which corresponds to all patient IDs ≤8056). This led to two counts of enrolled HIV-infected subjects: the first from the main study including 100 and 109 subjects in the 9INH and 3RPT/INH groups, respectively and the second including 93 and 97 subjects in 9INH and 3RPT/INH groups, respectively (all MITT) leading to a total of 193 and 206 HIV-infected subjects (ITT: 195 and 208, 9INH and 3RPT/INH, respectively) (Table 10). Overall, the numbers of subjects per treatment group did not differ greatly within each specific analysis population; however, the proportion of subjects in the safety population was higher in the 3RPT/INH group compared to the 9INH. This imbalance is driven by the open-label study design and the possibility that knowledge of treatment assignment might have led to some subjects in the 9INH group failing to take assigned treatment

Table 10. HIV Sub-Trial Analyses Populations

HIV Seropositive	3RPT/INH	9INH
ITT^	***208***	***195***
Main study	110* (52.9)	102 (52.3)
Extension period	98 (47.1)	93 (47.7)
MITT	***206 (99.0)***	***193 (99.0)***
Main study	109 (52.4)	100 (51.2)
Extension period	97 (46.6)	93 (47.7)
Safety	***207 (99.5)***	***186 (95.4)***
Main Study	109 (52.4)	95 (48.7)
Extension period	98 (47.1)	91 (46.7)

^First-enrolled ITT same as overall ITT in this sub-trial
*Four (4) subjects with HIV-seropositive status confirmed after enrollment (beyond 7 days after enrollment)
Main Study: enrollment up through Feb 2008
Extension including enrollment from Feb 2008 through Dec 2010 (beginning with USUBJID 8073)
Percentages are of the overall ITT

All enrolled subjects were at least 12 years of age (mean age between 36-37 years) and the majority were male gender, of Black or White race, had a history of alcohol abuse and enrolled at a US-based site (Table 11). Few subjects were recent TST converters, in close contact with a TB case, co-infected with hepatitis C or B virus or had a history of drug abuse. The only noted difference between treatment groups was a higher number of recent TST converters in the 3RPT/INH group compared to the 9INH group; however, the overall proportion was less than 10%, therefore having little impact on the overall results.

Table 11. Demographics and Characteristics (MITT Population, HIV Sub-Trial)

Variable	3RPT/INH (N=206) n (%)	9INH (N=193) n (%)
Mean age in years (sd)	37.1 (1.2)	36.6 (9.6)
≥18	203 (98.5)	192 (99.5)
12-17	3 (1.5)	1 (0.5)
Males	146 (70.9)	131 (67.9)
Race		
White	76 (36.9)	73 (37.8)
Black or AA	75 (36.4)	75 (38.9)
Asian, Native Hawaiian, Pacific Islander	6 (2.9)	3 (1.5)
American Indian/Alaska Native	5 (2.4)	4 (2.1)
Other/unknown	44 (21.4)	38 (19.7)
Country		
Brazil	49 (23.8)	35 (18.1)
Canada	5 (2.4)	1 (0.5)
USA	152 (73.8)	157 (81.3)
TST size (mm), mean (sd)	16.3 (7.2)	16.3 (9.8)
Close contact of a TB Case	22 (10.7)	25 (12.9)
Recent TST converter*	15 (7.3)	5 (2.6)
Fibrosis of chest X-ray	0	0
History of Alcohol Abuse	113 (54.8)	120 (62.2)
History of Drug Use	27 (13.1)	33 (17.1)
Homeless	22 (10.7)	22 (11.4)
Current Smoker	82 (39.8)	91 (47.2)
Hepatitis B Virus	22 (10.7)	26 (13.5)
Hepatitis C Virus	11 (5.3)	19 (9.8)
Enrolled as part of a cluster	0	0

*p-value=0.038 (Fisher's exact test)

4.2.1.1 HIV Sub-trial Findings

There were 2/206 (0.97%) and 6/193 (3.10%) cases of TB infection at the 33-month (MITT population) follow-up resulting in a cumulative failure rate of 1.01% and 3.45% in the 3RPT/INH and 9INH groups, respectively. The difference in cumulative failure was -2.44%, 95% CI (-5.50, 0.62). Few deaths were observed in this sub-trial, specifically, there were 1/207 (0.5%) and 4/186 (2.1%) deaths in the 3RPT/INH and 9INH in (safety population). There were no subjects enrolled as part of a cluster in this sub-trial so the MITT analysis is appropriate to assess treatment effect in this sub-group.

The incidence of TEAE hepatotoxicity was statistically significantly higher in the 9INH group compared to the 3RPT/INH group (5.9% versus 1.4%, respectively) (P=0.026), which is commensurate with hepatotoxicity findings in the overall main TBTC-S26 trial. TEAE hypersensitivity was numerically, but

not statistically significantly, more frequent in the 3RPT/INH treatment arm compared to 9INH (1.0% versus 0.0%, P=0.500).

4.2.2 TBTC-S26 Pediatric Sub-trial

The pediatric sub-trial was nested within the main TBTC-S26 trial; however, to increase the overall sample size pediatric enrollment was extended beyond the completion of enrollment in the main trial. The enrollment period began in February 2008 and ended in December 2010. Out of 1,058 enrolled pediatric subjects, 908 or between 85-86% met the requirements for the MITT population. The majority of subjects (70%) were enrolled during the main trial with no imbalances noted between groups (Table 12).

Table 12. Pediatric Sub-Trial Analyses Populations

	3RPT/INH	9INH
ITT	***552***	***506***
Main study	355	351
Extension period	197	155
First enrolled ITT	***438 (79.3)***	***419 (82.8)***
Main study	296	294
Extension period	142	125
MITT	***472 (85.5)***	***436 (86.2)***
Main study	322	316
Extension period	150	120
First Enrolled MITT	***375 (79.4)***	***367 (72.5)***
Safety	***539 (97.6)***	***493 (97.4)***
Main Study	348	342
Extension Phase	191	151

Extension period began on 2/16/2008
Percentages are of the overall ITT (all enrolled)

Among pediatric subjects in the MITT population, the average age was statistically significant higher (11.0 years) in the 9INH group compared to 3RPT/INH (10.3 years). In addition, there was a gender imbalance between treatment groups with more males enrolled in the 3RPT/INH group compared to the 9INH group. Finally, there were statistically significantly more subjects enrolled as part of cluster in the 3RPT/INH group (36.2%) compared to the 9INH control (28.2%), which is commensurate with the finding of an overall imbalance between groups with respect to enrollment as part of a cluster in the main TBTC-S26. This imbalance is a likely product of the open-label trial design and bias associated with knowledge of treatment assignment and serves to support the rational to focus on the first-enrolled MITT population instead of the MITT

Table 13. Demographics and Characteristics (MITT Population, Pediatric Sub-Trial)

Variable	3RPT/INH (N=472) n (%)	9INH (N=436) n (%)
Mean age in years (sd) *	10.3 (5.2)	11.0 (5.0)
2-11	235 (49.8)	180 (41.3)
12-17	237 (50.2)	256 (58.7)
Males^	258 (54.7)	201 (46.1)
Race		
White	341 (72.2)	298(68.3)
Black or AA	67 (14.2)	70 (16.1)
Asian, Native Hawaiian, Pacific Islander	35 (7.4)	49 (11.2)
American Indian/Alaska Native	2 (0.42)	2 (0.46)
Other/unknown	27 (5.7)	17 (3.9)
Country		
Brazil	55 (11.6)	50 (11.5)
Canada	1 (0.2)	13 (3.0)
USA	416 (88.1)	373 (85.5)
TST size (mm), mean (sd)	15.8 (8.4)	15.7 (7.0)
Close contact of a TB Case	433 (52.4)	394 (47.6)
Recent TST converter	77 (16.3)	80 (18.3)
Fibrosis of chest X-ray	0	0
HIV Seropositive	2 (0.4)	1 (0.2)
Current Smoker	10 (2.1)	14 (3.2)
Enrolled as part of a cluster#	171 (36.2)	123 (28.2)

*T-test for mean, p-value 0.04; Pearson Chi-Square for association between category and treatment, p-value=0.01
^p-value=0.01 (Pearson Chi-Square)
p-value<0.01 (Pearson Chi-Square)

4.2.2.1 Pediatric Sub-trial Findings

There were 0/472 (0%) and 3/436 (0.69%) TB infections in the pediatric sub-trial at the MITT 33-month follow-up in the 3RPT/INH and 9INH groups, respectively, leading to a 95% CI around the difference of proportions (3RPT/INH-9INH) of (-1.70, 0.28). The difference in cumulative TB infection rate was -0.78%, 95% CI of (-1.66, 0.10). TB infection counts in the first-enrolled MITT were 0/375 and 1/367 (0.27%) in the 3RPT/INH and 9INH groups, respectively resulting in a difference in the cumulative TB infection rate of -0.32%, 95% CI (-0.95, 0.31).

There were two deaths in the pediatric sub-trial population, both occurring in the 9INH group; however, neither death was associated with assigned treatment (see Medical Officer's review for a detailed summary of reported deaths).

Given the low number of events, sub-group efficacy analyses in the pediatric sub-trial were not feasible.

There were no reported events of hepatotoxicity in this sub-trial. There were 7 (1.3%) events of possible hypersensitivity reported in the 3RPT/INH group and zero events in the 9INH groups and all but one event was of Grade 1 or 2. All seven events were considered possibly or probably related to treatment and four led to permanent treatment discontinuation.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The following are the major statistical issues specific to the TBTC-S26 trial identified by the reviewer.

1. **Open-Label Design**: Ideally the TBTC-S26 trial could have been performed using a double-blind, double-dummy approach in which all subjects received a daily INH (or identical placebo) via self-administration for nine months and a once-weekly RPT and INH tablet (or identical placebos) via DOT for three months. This design would also standardize the frequency of trial assessments reducing bias between groups in ascertainment of safety outcomes. Likely, as a result of the open-label design there was an imbalance in number of subjects who took at least one dose of treatment favored the 3RPT/INH group (n=4040) compared to 9INH (n=3759). In addition, the enrollment into clusters differed across treatment arms and the randomization errors that occurred might have been due to knowledge of open label randomized treatment assignment.

2. **Clustered Enrollment**: The number of subjects enrolled as part of a cluster (not randomized) was larger in the 3RPT/INH (n=971) group compared to the 9INH group (n=718). To address the concern of clustering imbalances, both the applicant and reviewer considered an analysis of the primary endpoint in the first-enrolled MITT population; however, the reviewer considers this analysis as primary whereas the applicant considers it secondary. Overall, the findings of the first-enrolled MITT are consistent with those of the MITT population-both demonstrating that the 3RPT/INH group is non-inferior (margin of 0.091%) to the 9INH group.

3. **Death and LTF**: The 33-month lost to follow-up rate was between 10 and 11%, which leads to issues when attempting to infer the overall long-term efficacy of a treatment for LTBI. The applicant (and reviewer) performed multiple sensitivity analyses including LTF as failure and estimating numbers of potentially missed TB infections among those subjects who were LTF prior to reaching the event. None of these analyses led to results that greatly altered the overall conclusions. The proportion of subjects who died by 33-months post-enrollment in the MITT population was similar between groups: 0.8% and 1.0% in the 3RPT/INH and 9INH groups, respectively.

4. **NI margin Determination**: The applicant's approach to the margin derivation was based on the objective to show that the full 3RPT/INH regimen is effective by comparing it to the 9INH regimen and concluding non-inferiority with a margin as small as 0.24%. In contrast, the regulatory approach taken was based on the question as to if RPT contributes to the efficacy of 3RPT/INH. This led to an estimated NI margin of 0.091%. The TBTC-S26 met the primary endpoint demonstrating NI when using the FDA-derived margin of 0.091%, as well as the

applicant's larger margin.

5. **Observed TB Failure Rate in Control Group**: When assuming equal follow-up time up to 33-months post-enrollment (an ITT approach), the observed TB infection rate in the active control was approximately 0.15/100 person-years (PYs) (calculated as 15/(3745 persons*33/12 years follow-up (33-months))*100), which is markedly lower than the expected rate of 1.5/100 PYs used for trial design. Therefore, we can conclude that what was observed in the TBTC-S26 trial in the active control was lower than expected. However, the rate was similar to the previous findings from the IUAT trial used to support the NI margin providing some assurance that the constancy assumption is valid. Specifically, the IUAT-reported three-year incidence rates in 6 and 12 month INH regimens were 0.26 and 0.22 per 100 PYs, respectively (data on a nine month INH regimen unavailable).

6. **Randomization**: There were several randomization inconsistencies noted leading to skipped randomization codes or changes in baseline status (e.g. change in HIV status following randomization/enrollment or membership (part of cluster)). Overall, these inconsistencies were few in number relative to the overall sample size and likely have little impact the overall findings

7. **Trial Objective**: TBTC-S26 was originally designed with an equivalence objective based on a relative (to the expected TB rate in the control arm) margin of 50% (0.75% absolute difference) and changed to a non-inferiority objective based on a fixed margin of 0.75%. Thus, the primary hypothesis changed from a two-sided test of equality to a one-sided test of non-inferiority. The chosen non-inferiority margin was the same as the absolute difference of 0.75% stated under the original objective. Despite the change in primary objective, the overall results support a conclusion of non-inferiority of the 3RPT/INH regimen to that of the standard 9INH regimen within a conservative margin of 0.091%.

Regarding the supportive trial by Martinson et al (2011), the major statistical issues or concerns are firstly that subject-level data were not provided and therefore results cannot be replicated and, secondly, the trial was conducted at a single site in South Africa and enrolled mostly Black, women (all HIV seropositive) who were not receiving anti-retroviral therapy. Thus the results are not fully generalizable to the intended US population co-infected with HIV and latent tuberculosis.

5.2 Collective Evidence

The reviewer assessed data and findings from the large trial TBTC-S26, supportive sub-trials in HIV-seropositive subjects and pediatric subjects and findings from a published randomized, active-controlled trial.

The TBTC-S26 trial demonstrated that in adults and children (2 years of age or older) with confirmed LTBI that a three-month regimen containing rifapentine and isoniazid taken under direct observation and once-weekly led to a lower rate (at 33-month post-enrollment) of TB infection (0.18% or approximately 0.06/100 person-years) compared to a standard, nine-month isoniazid regimen self-administered daily (0.40% or approximately 0.15/100 person-years). The difference in cumulative TB rate was -0.24% with a 95% CI of -0.50, 0.01. In both treatment groups, the cumulative TB infection rate was lower than

estimated from previous studies or reports (approximately 1.5/100 person-years at 24 months) suggesting that there has been a possible change in the overall epidemiology of the disease or population at risk. In addition, the proportion of subjects completing treatment was statistically significantly higher in the 3RPT/INH group (84%) compared to the longer 9INH regimen (72%), which is likely associated with, and consequently biased by, the open-label design and different treatment regimens between 3RPT and 9INH (three vs. nine month duration, weekly vs. daily administration and directly-observed vs. self-administration, respectively).

The overall safety of the 3RPT/INH regimen was similar to that of the standard 9INH regimen with the exception of a finding of a higher incidence of possible hypersensitivity and a lower incidence of hepatotoxicity. There is evidence showing that rifampin can increase the risk of hypersensitivity reactions. Therefore, TEAEs of hypersensitivity in the RPT group were assessed in detail by the applicant and the review team. In addition, hepatotoxicity is a known risk associated with multiple TB regimens, including those including INH. Therefore, liver function and signs /symptoms of hepatotoxicity were routinely assessed throughout the trial. Specifically, the incidence of possible hypersensitivity TEAEs, with the majority leading to permanent drug discontinuation and of grade 3 or higher, was statistically significantly higher in the 3RPT/INH regimen (4%) compared to the 9INH regimen (0.5%). Incidence of hepatotoxicity was significantly higher in the 9INH group (3.0%) compared to the incidence in the 3RPT/INH group (0.6%).

Findings in the two TBTC-S26 sub-trials were consistent with findings in the main trial suggesting no apparent treatment-by-age or treatment-by-HIV-serostatus interactions. The overall safety profiles were similar as well.

Findings reported in a separate, randomized, open-label trial in South African HIV-seropositive LTBI subjects suggest that the cumulative incidence of TB infection in subjects treated with 3RPT/INH (DOT) is similar to that among subjects treated with a standard 6-month, daily, self-administered isoniazid regimen (approximately 2/100 person-years at 72 months follow-up in both groups). These data are only considered supportive since patient-level data were not provided in the submission thus preventing complete verification of the results.

Finally, RPT was approved in 1998 for treatment of active pulmonary tuberculosis based on findings from two, adequate and well-controlled clinical trials. These prior data, along with results from the TBTC-S26 trial (and supportive sub-trials) and an existing safety profiles, provide strong evidence that RPT is contributing to the efficacy found in the three-month RPT/INH regimen for treatment of LTBI.

5.3 Conclusions and Recommendations

After review of the submitted data and supporting documents, the reviewer concludes the following:

- The three-month, once-weekly, DOT RPT/INH regimen was shown to be non-inferior (within a 0.091% margin) to the standard nine-month, once-daily, self-administered INH regimen based on incidence of TB infection at 33-months post-enrollment in the MITT and in the first-enrolled MITT populations demonstrating the efficacy of RPT in the treatment of latent TB in a 3 month regimen with INH. However, due to notable imbalances between groups in cluster sizes, which

were likely a direct result of the open-label trial design, the reviewer recommends that the results in the first-enrolled, MITT should serve as primary for purposes of product labeling.

- Findings in the HIV and pediatric sub-trials were consistent with those found in the overall trial; however, HIV testing was not routinely performed in all subjects at time of enrollment and therefore the HIV sub-population may not fully resemble a LTBI/HIV co-infected population for whom this product will be marketed.
- Despite the occurrence of few TB infections, there was no evidence of drug resistance patterns in either treatment group.
- The incidence of possible hypersensitivity events, many of which were of grade 3 or higher and led to permanent drug discontinuation was significantly higher in the 3RPT/INH regimen versus 9INH control. Conversely, less events of hepatotoxicity were observed in the 3RPT/INH compared to the 9INH group.
- As would be expected given the open-label design and differing treatment duration and routes of administration, treatment completion rates were higher among subjects in the 3RPT/INH group compared to the standard 9INH group and there were no findings of increased drug resistance in either regimen.

In conclusion, a regimen of RPT/INH given once-weekly (DOT) for three months to patients with LTBI appears to be an effective (to prevent active TB infection) and safe regimen in adults and children two-years of age or older, and RPT was shown to significantly contribute to that efficacy. Guidance to prescribers and patients should be given with respect to the potential risk of hypersensitivity reactions and the requirement for directly-observed therapy.

5.4 Labeling Recommendations (as applicable)

The statistical reviewer and team leader recommended that the clinical studies section 14 present the TBTC-S26 primary efficacy results in the first-enrolled MITT population rather than the MITT population due to the noted imbalances between groups in enrollment by cluster (and cluster size). Also, the statistical reviewer recommended simplifying HIV and pediatric sub-trial findings, which were general commensurate with the overall trial findings.

References

Gordin FM, et al. Rifampin and pyrazinamide vs. isoniazid for prevention of tuberculosis in HIV-infected persons. An international randomized trial. JAMA 2000;283:1445-50.

International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. Bulletin of the World Health Organization 1982 , 60: (4):555-564.

Martinson NA, et al. New Regimens to Prevent Tuberculosis in Adults with HIV Infection. N Engl J Med 2011;365:11-20.

APPENDICES

6 Appendix A: Data Used in Non-Inferiority Margin Determination

The applicant's justification of the NI margin used data provided from two source: a Cochrane Review published in 1999 outlining a systematic review and meta-analyses to 6- and 12-month INH regimens for treatment of LTBI in non-HIV infected persons. The second source was published findings from the IUAT trial (Bulletin of the WHO, 1999) that compared placebo, 12-, 24-, and 52-week INH in a double-blind design. Both are summarized below.

Cochrane Review
Title: Isoniazid for preventing tuberculosis in non-HIV infected persons.
Citation: Smieja M, Marchetti C, Cook D, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database of Systematic Reviews* 1999, Issue 1. Art. No.: CD001363. DOI: 10.1002/14651858.CD001363.

Objective: To estimate the effect of six and 12 month courses of INH for preventing TB in HIV-negative people at increased risk of developed active TB.
Search Strategy: The Cochrane Infectious Diseases Group Specialized Register, CENTRAL, Science Citation Index, Cumulated Index Medicus, MEDLINE, EMBASE and reference lists of articles were search up to 2003.
Selection Criteria: RCTs of INH preventive therapy for at least six months compared to placebo with a follow-up for a minimum of two years. Trials including subjects with current or previously treated active TB or with unknown HIV infection were excluded. Search criteria were applied for two reviewers independently.
Main Findings: The search yielded eleven trials (Table 14) involving 73,375 subjects. Treatment with INH resulted in a pooled (random effects) risk ratio (RR) of developing active TB of 0.40, 95% CI (0.31, 0.52) over two years or longer. There was no difference between six and 12 months courses (RR 0.44, 95% CI 0.27 to 0.73 for six months (analysis 3.1 figure), and 0.38, 95% CI 0.28 to 0.50 for 12 months (analysis 4.1 figure)). Preventive therapy reduced deaths from TB but no difference observed for all-cause mortality. The rate of reported hepatotoxicity was 0.36% in the INH 6 month groups and 0.52% in the 12 month INH group.

Table 14. Trials Included in Cochrane Review

Publication	Methods	Participants	Interventions	Outcome	Comments
Comstock, 1962	Rand by family unit	7,333 Alaskan villagers	INH 300 mg x 1 yr	Active Tb	
Del Castillo, 1965	Rand by family unit	400 households in Philippines	INH 5-10 mg/kg x 1 yr	Active TB	
Egsmose, 1965	Rand by household	626 Kenyan rural villagers	INH 300-500 mg daily for 1-2 yrs	Pulmonary TB, Death	
Falk, 1978	Individual rand	7,036 men in US VA hospitals	INH 300 mg daily for 1-2 yrs	Active TB	Majority of this group had previous TB Rxs, 2,389 included in meta-analyses
Ferebee, 1962	Rand by family unit	25,033 household contacts of newly reported TB cases	INH 300 mg/kg or 5 mg/kg for 1 yr	Active TB, extrapulmonary TB, death	
Ferebee, 1963	Rand by ward or building	25,838 pts in 37 county institutions for chronically psychiatric or mentally retarded, Wisconsin, Georgia and Mass, USA	INH 300 mg daily for 1 yr	Active TB, death	91% normal chest x-ray, 9% abnormal at baseline
Girling, 1992	Individual rand	679 Chinese men w/silicosis in Hong Kong	INH 300 mg daily for 6 mos, Rifampin 600 mg daily x 12 weeks, INH+RIF x 12 weeks, placebo	Active TB	
John, 1994	Individual rand	184 transplant or dialysis subjects in India	INH 300 mg or placebo x 1 yr	Active TB, death, hepatitis	High rate of drop-out and hepatitis in both groups
Mount, 1962	Rand by family unit	2,824 household contacts of known TB cases in US, 1/3 children	INH 300 mg daily x 1yr	Active TB, extrapulmonary TB, death	
Thompson, 1982	Individual Rand	28,000 adults in Eastern Europe	INH for 3, 6, or 12 moths, placebo	Active TB, hepatitis	
Veening, 1968	Individual Rand	261 PPD positive contacts of active cases in Netherlands Navy	INH 600 mg for 4 mos then 400 mg daily for total of 1 yr	Active TB	

Rand=randomization

IUAT Trial

Citation: International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. Bulletin of the World Health Organization 1982, 60: (4):555-564.

Objective: To compare the relative effectiveness of shorter durations of INH preventive therapy in TBT-positive adult (20-64 years of age) patients with fibrotic lesions in seven European countries.
Treatment Assignment: Double-blind randomization to 12-weeks INH (n=6956), 24-weeks INH (n=6965), 52-weeks INH (6919), 12-week placebo (n=2350), 24-weeks placebo (n=2338) and 52 weeks placebo (n=2302).
Endpoint: culture-positive TB at five years post-randomization
Main Analysis: Cumulative incidence at 5-years per 1000 persons, groups were compared by calculating the relative risk (of 5-year incidence) using the 52-week INH as the referent group
Findings: The 5-year incidence in the placebo, 12-INH, 24-INH and 52-INH groups was 3.6, 5.0, 11.3, and 14.3 per 1000 persons, respectively. This corresponds to a relative risk in placebo, 12-INH, and 24-INH groups (v. 52-INH) of 4.0, 3.1, and 1.4, respectively. The figure below (extracted from the publication) illustrates the annual incidence of TB infections per 1000 person across the 5-year time period. ***NOTE: This figure was used by Dr. Li to estimate the 3-year incidence in the 12-week and 24-week INH groups for purposes of determining the NI margin.***
Conclusions: The 12-INH eliminates, at most, one-third of TB cases that would occur without treatment; two-thirds of preventive value of INH therapy is achieved after six months of treatment; compared to 52-INH, 24-INH led to a 40% increase in number of TB cases at 5-years.

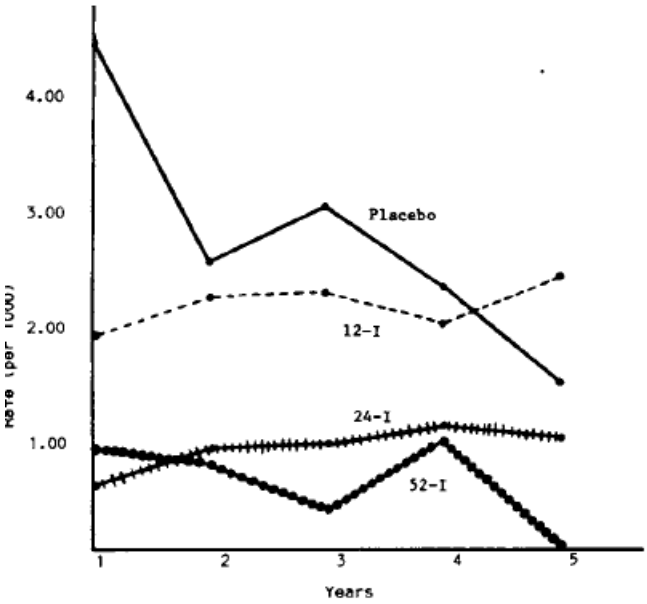


Fig. 1. Annual incidence of culture-positive tuberculosis: all participants, by regimen.

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/s/

LAREE A TRACY
11/04/2014

KAREN M HIGGINS
11/05/2014
I concur.