CLINICAL REVIEW

Application Type	NDA
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Priority or Standard	Priority
Submit Date(s)	May 30, 2014
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Division / Office	DAIP/OAP
Reviewer Name(s)	Hala Shamsuddin MD
Review Completion Date	October 23, 2014
Established Name	Rifapentine
Trade Name	Priftin™
Therapeutic Class	Anti-tuberculous rifamycin
Applicant	Sanofi-aventis US
Formulation	150 mg oral tablet
Dosing Regimen	900 mg once weekly for 3 months
Indication	Treatment of latent TB infection LTBI
Intended Population	Adults and children >2 years of age at high risk for TB disease

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommendation is to approve rifapentine, given weekly in combination with isoniazid by directly observed therapy for 12 weeks, in the treatment of latent tuberculosis infection in adults and children >2 years of age who are at high risk for tuberculosis disease, including HIV infected patients.

In Study TBTC 26, the pivotal study to support this application, rifapentine plus isoniazid given weekly for 12 weeks (3RPT/INH) was non-inferior to isoniazid given daily for 9 months (9INH) in the prevention of active TB, with a non-inferiority margin 0.09%. The study primary endpoint was development of culture-confirmed TB in adults and culture-confirmed or clinical TB in children at 33 months post enrollment.

Similar effectiveness results were obtained in TBTC Study 26 pediatric extension study that enrolled subjects 2-17 years of age, and in TBTC Study 26 HIV extension study that enrolled HIV-infected subjects.

1.2 Risk Benefit Assessment

The benefits of rifapentine in combination with isoniazid outweigh the risks in non-pregnant individuals. In addition, the shortened duration of therapy of LTBI allows for directly observed therapy (DOT) and improved treatment compliance.

Treatment adherence and completion of the prescribed regimen were statistically significantly higher in patients receiving 3RPT/INH regimen than in patients receiving the 9INH regimen.

The frequency of hepatotoxicity was lower in the 3RPT/INH arm compared to the 9INH arm. The main adverse reaction associated with 3RPT/INH administration was hypersensitivity reaction, manifesting mainly as flu-like illness, and occasionally as hypotension, bronchospasm, neutropenia, thrombocytopenia, urticaria and angioedema. The main reason to discontinue therapy in the 3RPT/INH arm was hypersensitivity reaction, while the main reason to discontinue therapy in the 9INH arm was hepatotoxicity. There were no cases of liver failure in either treatment arm. None of the deaths was drug related.

The frequency of hepatotoxicity was higher in both treatment arms in patients with HIV, HCV or HBV infection and in patients with history of alcohol use. There were no cases of hepatotoxicity in either treatment arm in children <18 years of age. The frequency of hypersensitivity reaction

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was considerably lower among HIV infected patients compared to the overall population enrolled; only one case occurred in an HIV infected adult.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None; Implementation of REMS elements other than labeling and Medication Guide is not necessary.

Priftin was FDA approved for the treatment of tuberculosis in 1998. Warnings in the product labeling mainly pertain to hepatotoxicity, hypersensitivity reactions and drug-drug interactions, including interaction with hormonal contraception. Other safety issues in the product labeling include (b) (6), body fluid discoloration, exacerbation of porphyria, and *Clostridium difficile* infection. These safety issues are adequately addressed in the product labeling and can continue to be adequately addressed by product labeling and Medication Guide. In addition, because the recommendation is for administration by DOT for the treatment of TB or the treatment of LTBI, Priftin distribution will be essentially controlled, mainly by state TB control centers which are under the management of the state departments of health.

1.4 Recommendations for Postmarket Requirements and Commitments

None; no new adverse events were noted that were not already included in the approved Priftin labeling.

2 Introduction and Regulatory Background

Latent TB infection (LTBI) is infection with *Mycobacterium tuberculosis* manifested by a positive TB skin test or interferon gamma release assay, but without symptomatic, radiologic or microbiologic evidence of replicating organisms indicative of active tuberculosis.

The CDC estimates the prevalence of LTBI in the US to be 11.2 million people. Without treatment, TB disease is expected to develop in 5-10% of these individuals, with the greatest risk occurring during the 6-18 months after skin test conversion and during periods of immunocompromise, in young children, HIV-infected individuals, injection drug users, patients with radiologic findings consistent with prior TB, patients who are > 10% underweight, patients with certain underlying diseases such as silicosis, diabetes, chronic renal failure, jejunoileal bypass, and patients with cancer of the head or neck[1].

1 CDC. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis infection. Mortality and Morbidity Weekly Report June 9, 2000, Vol.49/No.RR-6

The World Health Organization (WHO) estimates that globally 8.6 million people developed active TB and 1.3 million people died from TB in 2012[2]. Treatment of LTBI is a key component of TB control programs in the US and globally. The standard regimen for the treatment of LTBI is 300 mg daily isoniazid (INH) monotherapy for 9 months (270 doses), with an effectiveness in preventing TB disease within 2 years of treatment completion of approximately 65% (42-69%)[3]. INH therapy is limited by poor adherence and hepatotoxicity. Rifampin 600 mg daily for 4 months may be used, but although of shorter duration, is also limited by poor adherence and hepatotoxicity[4]. In addition, rifampin has many drug-drug interactions. A 2 months regimen of rifampin plus pyrazinamide is no longer recommended due to unacceptable rates of severe hepatotoxicity leading to hospitalization and death.

The sponsor is seeking approval of Priftin™, given weekly in combination with INH for 12 weeks, in the treatment of LTBI in adults and children ≥2 years of age who are at high risk of progression to TB (including close contacts of a patient with active TB, recent conversion to a positive tuberculin skin test, HIV-infected patients, or those with pulmonary fibrosis on chest radiograph). This dosing regimen allows for directly observed therapy (DOT).

2.1 Product Information

Priftin™ (rifapentine) is a rifamycin that was initially FDA approved in June 1998 for the treatment of pulmonary tuberculosis caused by susceptible isolates of *M. tuberculosis*, in combination with one or more antituberculosis drugs in adults. The approved dose is 600 mg twice weekly for the initial two months given by DOT with an interval no less than 3 consecutive days between doses, followed by 600 mg once weekly by DOT for the 4 months continuation phase. The product labeling states that Priftin has not been studied as part of the initial phase treatment in HIV positive patients with pulmonary tuberculosis, and also should not be used as once weekly in the continuation phase of TB treatment in HIV infected individuals due to higher relapse rates (b) (4) The product labeling cautions regarding use in patients with cavitary disease due to higher incidence of failure or relapse.

Priftin™ labeling contraindicates the drug in patients with history of hypersensitivity reaction, but the signs and symptoms of such a reaction are not described. The main adverse reactions included in the Warnings section of labeling include hepatotoxicity, discoloration of body fluids, *C. difficile* associated diarrhea and drug-drug interactions due to CYP450 enzyme induction.

2 WHO global report 2012 accessed at http://www.who.int/tb/publications/global_report/gtbr13_main_text.pdf
3 Smieja M, Marchetti C, Cook D, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Database of Systematic Reviews Issue 1, 2010
4 Sharma S, Sharma A, Kadhiravan T, Tharyan P. Rifamycins (rifampin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Cochrane Database of Systematic Reviews 2013, Issue 7

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Other adverse reactions occurring in ≥10% of patients include hyperuricemia, (b) (4) hematuria, (b) (4) proteinuria, lymphopenia, neutropenia, anemia and hypoglycemia.

For the indication of treatment of LTBI, rifapentine will be administered with isoniazid (INH). INH is approved for the treatment of drug-susceptible TB in combination with other antituberculosis drugs, and for the prevention of TB in persons with HIV infection, close contacts of persons with newly diagnosed TB, recent TB skin test converters and persons with certain comorbidities that increase the risk for TB. INH product labeling includes a boxed warning regarding the risk of hepatitis. The warning states that severe and fatal hepatitis has been associated with INH exposure, and that the risk is age-related: <1/1000 for persons under 20 years of age, 3/1000 for persons 20-34 years of age, 12/1000 for persons 35-49 years of age, 23/1000 for persons 50-64 years of age and 8/1000 for persons over 65 years of age. Product labeling also contraindicates the drug in patients who develop hypersensitivity reaction, including hepatitis or drug fever, chills, and arthritis. A Cochrane Collaborative review reported the rate of hepatotoxicity associated with INH to be 0.36% for 6 month regimen and 0.52% for 12 month regimen[3].

Isoniazid and rifapentine are both pregnancy category C. Priftin labeling states that the drug is embryotoxic in rats at 0.6x the human dose (human dose (b) (4) presumably refers to the approved 600 mg twice a week) based on body surface area. Rats given rifapentine during organogenesis delivered pups with cleft palate, right aortic arch, increased incidence of delayed ossification and increased number of ribs. Pregnant rabbits exposed to 0.3-1.3x the human dose (based on BSA) produced pups with major malformations including ovarian agenesis, microphthalmia and ossified facial structures. INH labeling states that the drug is embryocidal in rats and rabbits, but does not provide exposure data. Labeling of (b) (4) drug does not include recommendations for birth control.

2.2 Tables of Currently Available Treatments for Proposed Indications

The standard regimen for the treatment of adults with latent TB is 9 months of 300 mg daily isoniazid. Rifampin given daily for 4 months may also be used. A 2-month regimen of daily rifampin plus pyrazinamide is no longer recommended due to excessive hepatotoxicity. In 2011, the CDC recommended weekly INH plus rifapentine given by DOT for 3 months as an equal alternative to 9 months of INH in patients ≥12 years of age[5,6].

5 http://www.cdc.gov/tb/topic/treatment/ltbi htm
6 CDC, Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection MMWR 2011;60(48);1650-1653

Table 1: Latent TB Infection Treatment Regimens

Drug	Regimen	Comments
Isoniazid (INH)	Daily for 9 months	FDA approved for LTBI treatment Hepatotoxicity Low compliance
Rifampin (RIF)	Daily for 4 months	Hepatotoxicity Drug-Drug Interactions
Rifampin plus Pyrazinamide (RIF/PZA)	Daily for 2 months	No longer recommended due to severe hepatotoxicity
Isoniazid plus Rifapentine (INH/RPT)	Weekly for 3 months	Regimen is the subject of this review. Recommended by CDC in 2011 as an alternative to Isoniazid Lower hepatotoxicity compared to isoniazid for 9 months Higher treatment adherence and completion compared to daily isoniazid Associated with hypersensitivity reactions

2.3 Availability of Proposed Active Ingredient in the United States

Rifapentine is marketed in the United States as 150 mg tablets under the brand name Priftin™. Isoniazid is marketed in the United States under multiple generic brands.

2.4 Important Safety Issues With Consideration to Related Drugs

The main safety concerns associated with rifamycin exposure are hypersensitivity reactions, hepatotoxicity and drug-drug interactions.

Rifamycin hypersensitivity reactions are generally associated with high or intermittent rifamycin exposure. They are thought to be immune-mediated and usually manifest as a flu-like illness. The onset of symptoms typically occurs within 1 to 2 hours after ingestion. Common manifestations include fever, rash, urticaria, (b) (4) and diarrhea. Less frequent

manifestation may include thrombocytopenia, [redacted] (b) (4) respiratory symptoms and shock.

Rifamycins are CYP3A4 and 2C8/9 inducers and thus may have several drug interactions, including several anti-retroviral therapies and hormonal contraception.

Other safety issues include *Clostridium difficile* colitis and discoloration of body fluids.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The pivotal study in this submission, TBTC Study 26, was planned and conducted by the TB Trial Consortium of the CDC.

TBTC Study 26 protocol was submitted on March 9, 2001 to IND 46,954 held by the CDC. The study was randomized and open-label, designed to evaluate the effectiveness of daily INH 300 mg for 9 months to weekly INH 900 mg plus rifapentine 900 mg for 3 months in the treatment of latent TB infection in high risk individuals. The FDA recommended a blinded, double-dummy study that would include the two treatment arms as described plus a third arm treated with INH 900 mg weekly for three months. The CDC stated that the addition of a 900 mg INH monotherapy arm in a double-dummy design as suggested by the FDA would be logistically unfeasible because of the difference in dosing and duration of the regimen and would also substantially increase the pill burden.

A protocol amendment was submitted in 2005 regarding further enrollment of children, and a statistical analysis plan was submitted in October 2010. The CDC/TBTC and the FDA met on May 25, 2011 to discuss the study results. In that meeting, the TBTC stated that in addition to their initial feasibility concerns regarding adding a third treatment arm of INH 900 mg administered weekly for three months, they also considered using this short monotherapy weekly regimen to be unethical based on the poor effectiveness of 300 mg daily INH for 3 months and the short half-life of INH. During the meeting, the CDC indicated that the TBTC Study 26 data will be given to Priftin manufacturer, Sanofi, for a regulatory submission to seek the indication of treatment of latent TB infection.

Sanofi submitted a pre-NDA meeting package to IND 45,138 on August 2, 2012. Sanofi indicated that they were aware of the discussions between the FDA and the CDC and intended to cross reference the CDC's IND 46,954. Sanofi proposed using TBTC Study 26 as the pivotal study and two publications reporting studies conducted in South Africa[7] and Brazil[8] as supportive evidence. The FDA found the proposal acceptable and recommended that a non-

7 Martinson NA et al. New regimens to prevent tuberculosis in adults with HIV infection. NEJM 2011;365:11-20
8 Schechter M et al. Weekly rifapentine/isoniazid or daily rifampin/pyrazinamide for latent tuberculosis in household contacts. Am J Respir Crit Care Med 2006;173:922-926

inferiority margin justification be submitted for review prior to the sNDA submission. The FDA also recommended submitting a proposed plan to handle missing data. These were submitted on February 22, 2013.

2.6 Other Relevant Background Information

License to Cross-Reference CDC Data and Study Report
A memo from the CDC was included in this submission giving sanofi-aventis U.S. LLC the license to cross reference IND 46,954 and the Clinical Study Report submitted to that IND on August 7, 2012, as well as the license to use all additional data related to TBTC Study 26, including but not limited to the study datasets and all the addendums to the TBTC Study 26 CSR, for use in regulatory submissions to the FDA.

Pediatric Study Plan
There is no pediatric formulation. Priftin is supplied as a 150 mg film-coated tablet. In clinical studies, the tablet was crushed and administered as slurry with a starch based pudding.

The sponsor contended that the PK and efficacy information submitted in this NDA satisfied PREA requirements for children 2-17 years of age. The sponsor requested partial waiver of PREA required studies in children from birth to 2 years of age because the small number of patients with LTBI in this age group and their geographic dispersion in the United States make clinical studies impracticable.

There are no epidemiologic data for LTBI cases in children <2 years of age. However, in 2010, there were 365 cases of active TB in the US in children <4 years of age. Approximately 35% of pediatric TB cases occur in California and Texas, and the remaining 65% are dispersed throughout the US[9].

The rate of progression from LTBI to disease is presumed to be 5-10% in adults. Rates of progression are higher in children, estimated at 43% for infants less than 1 year of age, and 24% for children 1-5 years of age[10]. The number of children < 2 years of age with LTBI is therefore estimated to range from 730-1460.

9 Epidemiology of Pediatric Tuberculosis in the United States, 1993–2010.Surveillance, Epidemiology, and Outbreak. Investigations Branch, Division of Tuberculosis Elimination, Centers for Disease Control and Prevention (CDC).
http://www.cdc.gov/tb/publications/slidesets/pediatrictb/default.htm

10 Menzies HJ, Winston CA, et al. Epidemiology of Tuberculosis Among US- and Foreign-Born Children and Adolescents in the United States, 1994–2007. Am J Public Health.
2010;100(9):1724–1729

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The PSP was discussed with the Pediatric Review Committee on September 10, 2014. A waiver of pediatric studies was granted in children <2 years of age. PK, tolerability, safety and efficacy results from Study 26 pediatric extension study were considered adequate to satisfy PREA requirements in older children.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

TBTC protocol and amendments, and the informed consent document were submitted to and approved by the CDC Institutional Review Board and by each site's local Independent Ethics Committee/IRB prior to study initiation.

All adult subjects provided informed consent and received a copy of the signed consent form. Guidelines established by the Office of Human Research Protection were followed for vulnerable patients, such as children < 18 years of age and persons who do not read English. Assent from children < 18 years of age and permission from one of their parents or legal guardians were obtained in accordance with CFR part 46.405. A copy of the informed consent document was provided in the submission.

An independent Data Safety Monitoring Board (DSMB) composed of TB experts external to CDC (the study sponsor) or Sanofi (the sNDA applicant) reviewed the safety data on an ongoing basis. An independent external Clinical Events Committee consisting of three TB experts reviewed all suspected or confirmed TB cases. Members were blinded to the assigned treatment.

All clinical work conducted under this protocol was subject to the FDA's IND regulations for GCP, the regulations of Canada's Therapeutic Products Directorate, and other foreign regulatory authorities. Each clinical investigator agreed to the inspection of study-related records at any time by government regulatory agencies and by (b) (4) the study sponsor's Contract Research Organization (CRO). Monitoring of investigative sites was conducted according to a detailed monitoring plan. The frequency of the interim visits varied based on the number of patients enrolled. Initially, all sites were inspected every 6 months with the exception of Site 20/North Texas, which had a visit every 3 to 4 months. During the last 2 years of the study, some sites had one visit a year, based on either low enrollment or their prior documented high performance and the fact that over 30% of charts had already been monitored as per the site monitoring plan.

Pharmacy audits were conducted once a year at all sites over the course of the study.

3.2 Compliance with Good Clinical Practices

The study reports included a statement that the studies were conducted in compliance with Good Clinical Practice guidelines, and where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents.

All clinical study protocols and amendments were approved by Institutional Board Review committees.

3.3 Financial Disclosures

TBTC study 26 that supports this sNDA was planned, sponsored and conducted by the CDC. The study was not initially intended to be a registrational study and was not planned with the expectation that it would be used to support seeking a new indication or a change in Priftin labeling.

The CDC granted Sanofi the right to TBTC Study 26 data and Clinical Study Report to use in support of this regulatory submission. At the request of Sanofi, the CDC solicited financial disclosure forms from the study investigators and sub-investigators after the study was concluded. Only 105 forms out of 600 individuals named on the FDA 1572 form (approximately 18%) were returned. None of the returned forms reported financial interests. The CDC did not release the available financial disclosure forms to Sanofi at the advice of legal counsel, but the CDC indicated that it will release the forms directly to the FDA if requested. This submission includes a letter from the CDC attesting to the above, and stating that Sanofi's role in Study 26 was limited to providing rifapentine for the trial free of charge.

Sanofi informed the FDA during the pre-NDA meeting that financial disclosure forms will not be submitted. The submission includes an attestation from Sanofi that they were not involved in the planning or conduct of TBTC Study 26, that they are unaware of any particular financial arrangements between the CDC and TBTC Study 26 investigators, and that the investigators were not compensated by Sanofi for any activities related to the conduct of Study 26.

Reviewer's Comments
The study was conducted by the TBTC of the CDC, a federal agency with no financial interests in the study outcome. The CDC attested that the applicant was not involved in the design or conduct of the study and was not involved in the original data analysis.

The applicant has adequately disclosed financial arrangement with the CDC and the study investigators and has satisfactorily demonstrated due diligence in tracking financial disclosure forms.

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The financial disclosure template is appended to this review (Section 9.3).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC information was submitted in support of this efficacy supplement. Priftin was provided by Sanofi to the CDC after a cooperative research and development agreement. The product used in clinical studies was the same formulation as the approved 150 mg tablet, and manufactured according to the same specifications and the same manufacturing site as the formulation marketed in the United States.

4.2 Clinical Microbiology

No new microbiologic data were submitted other than what is already included in Priftin labeling.

4.3 Preclinical Pharmacology/Toxicology

No new toxicology data were submitted in support of this application other than what is already included in Priftin labeling.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Similar to other rifamycins, rifapentine inhibits the beta subunit of bacterial DNA-dependent RNA polymerase, sterically blocking the elongating RNA transcript leading to abortive transcription. It is bactericidal against susceptible strains of *M. tuberculosis*.
Acquired resistance is the result of one of several single step mutations within the *rpoB* gene that encodes the beta subunit of the RNA polymerase. Rifamycin resistance due this gene mutation appears at approximately 10^{-8}.

4.4.2 Pharmacodynamics

No pharmacodynamic studies were submitted.

4.4.3 Pharmacokinetics

No new information was submitted regarding the PK profile of Priftin in adults. A 600 mg dose results in a peak concentration of 8 to 30ug/mL, occurring 4 to 6 hours after ingestion. Administration with food increases bioavailability by approximately 50%. Rifapentine is 97.7% protein bound. It is mainly metabolized by CYP3A4, and is also an inducer of CYP3A4. Half-life is 14 to 18 hours.

PK study in a subset of children 2-11 years of age who were enrolled in TBTC Study 26 pediatric substudy and two new drug interaction studies (INT12099 and 12291) were included in this submission.

TBTC Study 26 Pediatric PK substudy

The pediatric dose used in the main Study was based on an algorithm. A nested PK substudy was included in Study 26 to compare RPT exposures in children given the weight-based dosing regimen to RPT exposures in adults given the 900 mg dose, and to evaluate the adequacy of RPT doses used in children 2-11 years of age.
80 children and 77 adults were analyzed. The mean RPT mg/kg dose was approximately two fold higher in children compared to adults (22.8 vs. 10.7 mg/kg). The geometric mean AUC of rifapentine was 31% higher in children compared to adults: 720 (674-769) mcg*h/mL in children and 551 (516-588) mcg*h/mL in adults. Exposure was lower in children 2-4 years compared to older children and lower in children administered the crushed tablet compared to the whole tablet. However, exposure remained higher than the exposure in adults.

Reviewer's Comments
Despite the higher exposure noted in children, the frequency of adverse events was not higher in children compared to adults. There were no cases of hepatotoxicity reported in children and a lower frequency of hypersensitivity reactions compared to adults (see Safety Evaluation).

INT12099

This study was an open-label, randomized, four-period, four-sequence, four-treatment crossover PK interaction study of a single dose of 900 mg rifapentine and a single dose of 900 mg isoniazid in healthy male and female subjects. The study was conducted between May and June 2011.

Seventeen (17) subjects were enrolled and 15 completed the study. There was no significant interaction under fasted conditions: co-administration of rifapentine and isoniazid did not result in change in exposure compared to administration of each drug alone. Under fed conditions, co-administration of INH and RPT resulted in an increase of rifapentine exposure and a decrease in

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INH exposure: RPT Cmax increased by approximately 47% and AUC by 51% (with a similar increase of 25-DRPT metabolite), INH Cmax and AUC decreased by 46% and 23% respectively.

INT 12291

This was an open-label, non-randomized, single sequence, two periods, four-treatment, three parallel groups PK study to evaluate the interaction of repeated daily or weekly doses of rifapentine on Atripla™ in HIV infected patients. Atripla is a fixed dose combination of efavirenz, emtricitabine and tenofovir.

This study was conducted between December 2012 and June 2013. Subjects were to be enrolled in 3 cohorts:

- Cohort 1: Atripla for 15 days followed by Atripla plus 15 mg/kg rifapentine daily for 21 days
- Cohort 2: Atripla for 15 days followed by Atripla plus 900 mg rifapentine once weekly for 3 weeks
- Cohort 3: Atripla for 15 days followed by Atripla plus 10 mg/kg rifapentine BID for 21 days

At the time of the study report, Cohort 3 was not started and Cohort 1 was ongoing. Only results from Cohort 2 were reported.

Twelve (12) HIV infected subjects were enrolled. Eleven (11) had been on Atripla for at least 3 months prior to enrollment and one had been on Atripla for 4 weeks prior to enrollment. Single dose rifapentine co-administration did not change the steady state exposure of efavirenz or emtricitabine components compared to administration of Atripla alone, but increased tenofovir Cmax by 23% without significant change in Cmin or AUC0-24. After the third week of weekly rifapentine 900 mg administration, the steady state exposure of efavirenz, emtricitabine and tenofovir were comparable to the steady state exposure when Atripla was administered alone.

5 Sources of Clinical Data

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5.1 Tables of Studies/Clinical Trials

Table 2: Clinical Studies Submitted in Support of NDA for Rifapentine in the Treatment of LTBI

Study	Primary Objective	Design	Population	Primary Endpoint	N ITT/MITT/ Safety	Comments
Clinical Studies						
TBTC Main Study 26	Effectiveness and safety of RPT/INH weekly for 3 months (3RPT/INH) compared to INH daily for 9 months (9INH) in preventing TB disease in high risk tuberculin reactors	Multicenter Randomized Open-label Non-inferiority CDC proposed NI margin 0.75% Sanofi proposed NI margin 0.35%	Adults and children >2 years of age HIV-infected and HIV-negative persons	Culture-confirmed TB in adults or culture-confirmed or clinical TB in children at 33 months post-enrollment	3RPT/INH 4145/3986/ 4040 9INH 3908/3745/ 3759	Conducted in 23 centers in US, 3 centers in Canada and one center each in Brazil and Spain Weight based RPT dose Age based INH dose RPT/INH given by DOT INH self-administered
TBTC 26 Pediatric Extension Substudy	Effectiveness and safety in children Extended Study 26 to reach target pediatric population	Multicenter Randomized Open-label Evaluate safety and tolerability of 3RPT/INH	2-17 years of age	Safety and Tolerability Effectiveness: Culture confirmed or clinical TB	3RPT/INH 552/472/539 9INH 506/436/493	29 Study Centers (US, Canada, Brazil, Hong Kong, China, Spain) PK substudy in children 2-11 years of age
TBTC 26 HIV Extension Substudy	Effectiveness and safety substudy in HIV infected Extended Study 26 to achieve target HIV population			Culture confirmed TB in adults and culture confirmed or clinical TB in children	3RPT/INH 208/206/207 9INH 195/193/186	36 Study centers in US, Canada, Brazil, Spain, Hong Kong, and Peru
Martinson et al[7].	Safety and efficacy of 3RPT/INH 900/900 mg weekly for 3 months	Multicenter Randomized Open-label Superiority design	HIV-infected Individuals	TB disease or death	3RPT/INH 329/328 (MITT/Safety) 3RIF/PZA 329/329	Conducted in South Africa Copy of published article

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	compared to 3 other regimen: 3RIF/INH 600/900 twice weekly, INH 300 daily for ≤6 years, or INH 300 daily for 6 months in preventing TB disease in HIV-infected patients with positive tuberculin skin test				6yINH 164/164 6mINH 328/327	submitted
Schechter et al[8].	Safety of 3RPT/INH 900/900 weekly vs. 2RIF/PZA daily in preventing TB in household contacts of patients with pulmonary TB	Multicenter Randomized Open-label	HIV-negative Individuals	TB disease	3RPT/INH 206 2RIF/PZA 194	Conducted in Brazil Copy of published article submitted Study halted early due to excess hepatotoxicity in RIF/PZA arm
PK Studies						
Study INT12099	PK study to assess effect of single dose 900 mg RPT on single dose 900 INH	Single center, four-period, four-sequence, four-treatment crossover	Healthy subjects		17	
Study INT12291	PK study to assess effect of RPT on Atripla™	Single center parallel cohorts planned	HIV infected subjects with CD4>350 and undetectable viral load		12	Atripla x 15 days followed by Atripla plus 900 mg RPT per week for 3 weeks.

TBTC main Study 26 enrolled adults and children and HIV-infected and non-infected subjects. Enrollment of children and HIV-infected persons was extended after the main study was closed. The children enrolled in the main study were added to the children enrolled in the pediatric extension substudy for analysis. Similarly, HIV infected subjects enrolled in the main study were included in the analysis of the HIV substudy. This resulted in population overlap, as shown in the Venn diagram.

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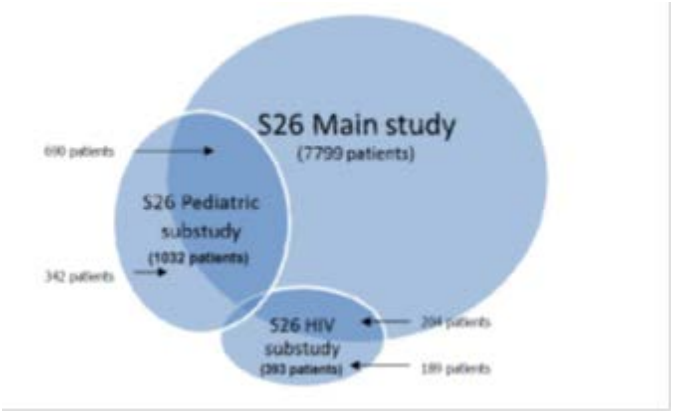
Figure 1: Venn Diagram of the Safety Population in TBTC Study 26 and the Pediatric and HIV Substudies



Note: Five children included in the pediatric substudy were HIV-infected at enrollment and were therefore also included in the HIV substudy. Of these 5 children, 1 child was enrolled in the TBTC-S26 main study, and the remaining 4 children were enrolled during the extended enrollment for the pediatric and HIV substudies.

5.2 Review Strategy

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 TBTC Study 26 Main Study

Study Description
The study was conducted by the Tuberculosis Trial Consortium, Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, between June 2001 and November 2010 at 28 study centers: 23 in the US, 3 in Canada and one each in Spain and Brazil. Findings of this study have been published[11].

The primary objective of the study was to compare the effectiveness of a three-month (12 doses) regimen of weekly rifapentine and isoniazid (3RPT/INH) to the effectiveness of a nine-month (270 doses) regimen of daily INH (9INH) in preventing TB in high-risk tuberculin skin test (TST) reactors. The study was originally designed to demonstrate equivalence of the two treatment regimens in preventing TB disease at 33 months after enrollment, where TB disease was defined as culture-confirmed TB in adults and culture–confirmed or clinical TB in children <18 years of age. The study was later changed to demonstrate non-inferiority of 3RPT/INH to 9INH at a NI margin of 0.75%.

11 Sterling TR, Villarino ME, Borisov AS, et al, and the TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 2011;365(23):2155-66

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The secondary objectives were to compare the rates of development of culture-confirmed or clinical TB at any age, drug discontinuation due to treatment related adverse reactions, drug discontinuation due to any reason, rates of grade 3, 4, or 5 drug related toxicities, treatment compliance rates, effectiveness and tolerability in HIV infected patients and effectiveness and tolerability in children <18 years of age.

High risk TST reactors screened for enrollment included household and other close contacts of active TB cases, recent (within 2 years) converters, persons with fibrotic lesions on CXR, HIV-infected individuals and young children. Close contacts were defined as persons spending at least 4 hours in a shared airspace during a one week period with a person with culture-confirmed TB disease. Children between 2 and 5 years of age and HIV-infected individuals who were close contacts of a person with active TB were eligible regardless of TST status.

At the time of screening, subjects were evaluated to rule out active TB, and to assess the risk of underlying liver disease (alcohol, IV drug use, self-report of hepatitis, women < 3 months post-partum). A pregnancy test for women of reproductive potential was obtained. Baseline lab tests included CBC with platelets, AST, and total bilirubin for the first 644 subjects enrolled and for subjects at high risk of liver toxicity. Baseline CD4 count was obtained for subjects known to be HIV-infected.

Subjects who met the inclusion criteria were randomized to receive 12 directly observed doses of RPT plus INH once weekly, or 270 doses of INH given once daily. Close contacts from the same household (clusters) were assigned to the same treatment arm to which the first subject was randomized. Subjects randomized to the INH arm were given a one month supply of medication and instructed to report to the clinic every 4 weeks. Treatment adherence in the INH arm was assessed by pill count. Treatment in the RPT/INH arm was directly observed (DOT). Patients were followed every 4 weeks until the end of assigned therapy, then every 3 months until the 21st month after enrollment then every 6 months until study completion. Patients who discontinued therapy due to rifapentine toxicity could be switched to 9INH. Patients who discontinued therapy due to INH toxicity were treated for latent TB at the discretion of the investigator.

Subjects who developed any signs of symptoms suggestive for TB were evaluated radiologically and by sputum samples for AFB smear and mycobacterial cultures. An independent Clinical Events Committee that was blinded to the assigned treatment adjudicated all cases of suspected or confirmed TB.

Rifapentine was dosed by weight. INH dosing in the monotherapy and combination arm was by age. For children or participants unable to swallow tablets, RPT was given crushed by slurry with a starch-based pudding (a fruit-based carrier was not recommended), and INH was given as liquid or pills crushed and mixed with RPT. Pyridoxine 50 mg was administered with each dose of INH in both study arms.

Table 3: Rifapentine Weight-Based Dosing – TBTC Study 26

Weight	Rifapentine Dose	Dose Per Kg
10 – 14 kg	300 mg	21.4-30.0 mg/kg
14.1 – 25 kg	450 mg	18.0-31.9 mg/kg
25.1 – 32 kg	600 mg	18.8-23.9 mg/kg
32.1 – 50 kg	750 mg	15.0-23.4 mg/kg
> 50 kg	900 mg	≤18.0 mg/kg

Table 4: INH Age-Based Dosing – TBTC Study 26

Age	INH Dose (mg) rounded up to nearest 50 or 100 mg	
	RPT/INH arm	INH arm
≥ 12 years	15 mg/kg; 900 mg max	5 mg/kg; 300 mg max
2 - 11 years	25 mg/kg; 900 mg max	10-15 mg/kg; 300 mg max

Because of drug-drug interactions with rifamycins, antiretroviral therapy was not given to HIV-infected patients in either treatment arm until >90 days after enrollment and patients were to wait at least 7 days after the last dose of RPT before initiating therapy with a protease inhibitor or non-nucleoside reverse transcriptase inhibitor. For persons concomitantly receiving methadone and rifapentine, the methadone dose could be increased if the participant developed signs/symptoms of methadone withdrawal.

Inclusion Criteria

- Males or non-pregnant, non-nursing females
- ≥ 2 years of age
- Tuberculin (PPD) skin test (TST) reactors at high risk for developing TB but without evidence of active TB.
    - Household and other close contacts of persons with culture-confirmed TB who are TST - positive as part of a contact investigation conducted within two years of the date of enrollment.
        - Close contact is defined as ≥ 4 hours in a shared airspace during a one-week period.
        - Among close contacts, a positive TST is defined as ≥ 5 mm induration after 5 TU of PPD placed intradermally using the Mantoux technique.
    - TST converters - converting from a documented negative to positive TST within a two-year period: TST ≥ 10 mm within two years of a nonreactive test or persons with TST increase ≥10 mm within a two-year period.
    - HIV-seropositive, TST positive (≥ 5 mm induration)
    - Persons with ≥ 2 cm^2 of pulmonary parenchymal fibrosis on chest X-ray, no prior history of TB treatment, ≥ 5 mm induration on TST, and 3 sputum cultures negative for *M tuberculosis* on final report.

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- Children ≥ 2 but < 5 years old with ≥ 10 mm induration on TST, regardless of TB exposure history
- HIV-seropositive close contacts of persons with culture-confirmed TB, regardless of TST status or prior therapy for latent or active TB
- Children ≥ 2 but < 5 years of age with a negative initial TST who are close contacts of a culture-confirmed TB case
- Willing to provide signed informed consent, or when applicable, parental consent and participant assent

Exclusion Criteria

- Current confirmed culture-positive or clinical TB
- Suspected TB (as defined by the site investigator)
- Tuberculosis resistant to isoniazid or rifampin in the source case
- A history of treatment for >14 consecutive days with a rifamycin or > 30 consecutive days with INH during the previous 2 years
- A documented history of completing an adequate course of treatment for active TB or latent TB infection in a person who is HIV seronegative
- History of sensitivity/intolerance to isoniazid or rifamycins
- If determined, AST> 5x ULN
- Pregnant or nursing females
- Persons currently receiving or planning to receive HIV-1 protease inhibitors or non-nucleoside reverse transcriptase inhibitors in the first 90 days after enrollment
- Weight < 10.0 kg

Reviewer's Comments
The enrollment criteria for patients at high risk for developing TB are appropriate. Pregnant and nursing women were excluded, but there were no provisions for pregnancy prevention in women of reproductive potential.

Sample Size and NI Margin Calculations
CDC NI Margin Calculation
The original 2001 protocol was designed to show equivalence of the two treatment arms in preventing culture-confirmed TB in subjects ≥ 18 years old or culture-confirmed or probable (clinical) TB in subjects < 18 years old within 33 months of study enrollment. The TBTC assumed the overall rate of TB over 2 years in untreated high risk TST reactors to be 5%, the effectiveness of nine months of daily INH to be 70%, and loss to follow up of 15%. Approximately 4000 persons per arm will have 80% power to show a relative difference between the two arms of +/- 50%, with an alpha of 0.05.

In 2005, the Kaplan-Meier cumulative incidence of culture-confirmed TB among patients pooled from both treatment arms was 0.38% (standard error 0.12%). This TB rate was lower than

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expected, affecting the original sample size calculations and indicating that the study was no longer adequately powered to show equivalence. The study objective was changed to demonstrate non-inferiority of the experimental regimen to the standard regimen at a NI margin of 0.75%. Still assuming the overall rate of TB in untreated high-risk tuberculin reactors to be 5% and efficacy of 9INH to be 70%, the treatment effect of 9INH (M1) was calculated to be 3.5%. An M2 of 0.75% preserves approximately 80% of M1. The sample size was recalculated at 3200 persons per arm.

Sanofi NI Margin Calculation
In a submission to IND 45138, the applicant, Sanofi, proposed an NI margin of 0.35%.
The treatment effect of 9INH at approximately 3 years after start of therapy was estimated by two methods. The first method used the International Union Against TB study that was conducted from the late 1960s to mid-1970s in seven European countries[12]. A total of 28,000 persons with fibrotic pulmonary lesions compatible with TB were followed for 5 years after receiving 12, 24, or 52 weeks of preventive treatment with daily INH or matching placebo. The 5-Year TB incidences for the placebo, 12 weeks of INH, 24 weeks of INH, and 52 weeks of INH regimens were 14.3, 11.3, 5.0 and 3.6 per 1000 respectively. Compared with placebo, 12 weeks of INH reduced the incidence of active TB by 21%, 24 weeks of INH reduced the incidence of TB by 65%, and 52 weeks reduced the incidence of TB by 75%. The published article did not report incidence of TB at 3 years, and neither the applicant nor the CDC were able to recover the original data. The incidence of TB at 3 years was estimated from a graph that was included in the published article. The 3-year TB incidences for placebo, 12, 24 and 52 weeks of INH were estimated at 10.2, 6.6, 2.6 and 2.2 per 1000 respectively. The treatment effect of 24 week INH regimen was therefore estimated as 10.2-2.6 = 7.6 per 1000, 95% CI (4.9, 10.3). M1 was estimated as the lower end of the 95% CI at 4.9 per 1000, or 0.49%. Preserving 50% of M1 yielded M2 of 0.245%.

In the second method, the applicant estimated M1 by identifying all placebo-controlled trials that compared INH at a dose of at least 200 mg daily or 5 mg/kg for at least 6 months to placebo and where the endpoint was development of TB at no less than 2 years after end of therapy. Eleven trials were identified. These trials were also reviewed in a Cochrane Collaboration Review[3]. Meta-analysis of the data retrieved from the Cochrane Collaboration included 73,375 patients and yielded an INH treatment effect of 1.21% (95% CI 0.7, 1.7). Using the lower end of the 95% CI, M1 was estimated at 0.7%. Preserving 50% of M1 yielded M2 of 0.35%.

FDA NI Margin Calculation
The experimental regimen being evaluated in TBTC Study 26 is a combination of rifapentine and INH. To grant the indication for rifapentine in the treatment of latent TB infection, the

12 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

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contribution of rifapentine to the overall regimen should be demonstrated. The treatment effect of rifapentine (M1) should be estimated using the effectiveness of weekly 900 mg INH as putative placebo. M1 would be the difference between the effectiveness of 300 mg INH daily for 9 months and the effectiveness of 900 mg INH weekly for 3 months.

The effectiveness of 900 mg INH weekly for 3 months is not directly available from review of the literature, but the effectiveness of 300 mg daily for 3 months is available from the previously cited IUAT article. The half-life of INH is short (one to two hours in fast acetylators and two to five hours in slow acetylators). The exposure resulting from 900 mg weekly INH is therefore expected to be less than the exposure resulting from 300 mg daily INH. Conservatively, we can consider the effectiveness of 300 mg daily INH and 900 mg weekly INH to be the same, and use the available data regarding the effectiveness of 300 mg daily INH for 3 months as the putative placebo.

Dr. Xianbin Li (Division of Biometrics) provided the estimation of the putative placebo effect based on the published IUAT article.

Table 5: Estimated TB rates and cases by treatment arm based on Figure 1 from IUAT article

	Randomized	TB Rate per 1000			
	N	Year 1	Year 2	Year 3	3 year cumulative rate
Placebo	6990	4.462	2.538	3.015	10.015
12 weeks daily INH	6958	1.908	2.246	2.262	6.415
24 weeks daily INH	6965	0.569	0.892	0.923	2.385
52 weeks daily INH	6919	0.892	0.738	0.369	2.000

Because the article did not include a 9 months INH arm, the effectiveness of 6 months of daily INH was used instead. The difference between INH daily for 3 months and INH daily for 6 months is 6.415-2.385 = 4.010 per 1000 persons, 95% CI is (1.82, 6.21) per 1000 persons. Conservatively considering M1 to be the lower bound of the 95% CI, M2 of 0.91 per 1000, or 0.091%, preserves 50% of M1.

The NI margin accepted by the FDA is therefore 0.091%.

Reviewer's Comments
The TB event rates reported among placebo recipients in the IUAT article and in the Cochrane Collaboration review were much lower than the 5% rate assumed by the TBTC for sample size calculations. In the IUAT article, the TB event rate in the placebo arm was 10 per 1000, or 1%. TB rate among placebo recipients enrolled in the 11 articles cited in the Cochrane review was 557/33113 (1.68%).

In addition, the TB event rate among recipients of 6 months or 12 months of INH in the IUAT article was approximately 2 per 1000, or 0.2%, and the rate among INH recipients in the Cochrane Collaboration review was 239/40262 (0.6%). These rates are comparable to the rate reported in the main TBTC study 26.

Protocol Amendments
The original protocol was dated 30 March 2001. There were four amendments:

1. The first amendment was in 2004 and pertained to clarification of eligibility criteria for HIV infected persons, added baseline CD4 count for HIV infected persons, clarified number of allowed 3RPT/INH doses within a 28 day period, clarified follow up for patients discontinued from study therapy, and clarified the process of AE reporting.
2. The second amendment was in 2005 and added a hypersensitivity substudy, accounted for clustering in the analysis, added a definition for hepatotoxicity, extended inclusion to children 2-11 years old to the study population and added a population PK substudy in children.
3. The third amendment was in 2006 and pertained to change in study design from equivalence to non-inferiority.
4. The fourth amendment was in 2007 to extend enrollment for additional children <12 years of age and for additional HIV infected individuals.

Protocol Violations
Protocol violations mainly pertained to labs not done at baseline, labs not done in patients at risk for liver injury and missed visits. Overall, the protocol violations were balanced between the two study arms and none are expected to affect interpretation of efficacy or safety.

5.3.2 TBTC Study 26 Pediatric Substudy

The initial plan was to enroll 644 children in Study 26. Because this was not achieved, enrollment of children was extended after closing the main study and participating sites were expanded to 29 centers in the United States, Canada, Brazil, Hong Kong, China and Spain.

The primary objective was to compare the safety and tolerability of weekly rifapentine plus INH for 3 months (3RPT/INH) to daily INH for 9 months (9INH) in children between 2-17 years of age. The secondary objective was to compare the effectiveness of 3RPT/INH to 9INH in preventing TB disease.

Eligibility criteria, dosing of rifapentine and INH, definition of analysis populations, TB outcomes and AE monitoring and definition of treatment emergent AE were as described for the Main Study.

Reference ID: 3648146

5.3.3 TBTC Study 26 HIV substudy

The initial plan was to enroll 644 HIV infected individuals in the main TBTC Study 26. Because this was not achieved when the study was closed, enrollment of HIV-infected subjects was extended through September 2013. Enrollment sites were also expanded in collaboration between the TBTC and the AIDS Clinical Trial Group (ACTG) and the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) to 36 sites, 23 in US, 3 in Canada, 6 in Brazil, one in Hong Kong, 2 in Peru and one in Spain.

The primary objective of this substudy was to compare the safety and overall tolerability of 3RPT/INH given by directly observed therapy to 9INH self-administered in HIV infected patients at high risk for developing TB. The secondary objective was to evaluate the effectiveness of the two regimens in preventing TB disease.

Eligibility criteria, dosing regimen and study events and procedures were the same as for the main study. Treatment compliance, TB endpoints, analysis populations and treatment emergent AEs were defined as in the main study.

Sample size was determined as follows: in a study comparing 3 months of rifampin plus pyrazinamide (3RIF/PZA) to 6 months of INH (6INH) among HIV-infected individuals, 2.3% discontinued treatment due to adverse events in the rifampin containing regimen compared to 0.6% in the INH arm. Among HIV-negative subjects with silicosis, 5% discontinued 3RIF/PZA and 5% discontinued 6INH. Assuming rates of drug discontinuation of 1% in one arm and 5% in the other arm, 15% loss to follow up, 322 subjects per arm has 80% power to demonstrate equivalent tolerability with alpha 0.05. Because enrollment was slow, the DSMB evaluated the pooled data after 403 subjects were enrolled and concluded that this was adequate to meet the primary objective.

5.3.4 Martinson et al. Study

Reference: Martinson N., Barnes G., Moulton L., Msandiwa R., Hausler H., Ram M., McIntyre J., Gray G., Chaisson R. New Regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med 2011;365:11-20

The study protocol was approved by the IRBs of John Hopkins Medicine and the University of Witwatersrand, Medicines Control Council of South Africa and the FDA (IND 62,611). Written informed consent was obtained from all patients.

Reference ID: 3648146

This was a randomized, open-label study conducted in Soweto, South Africa comparing four LTBI treatment regimens in HIV infected individuals who had a positive TST and who were not receiving anti-retroviral therapy. The regimens were:

- rifapentine 900 mg plus INH 900 mg weekly for 3 months (3RPT/INH),
- rifampin 600 mg plus INH 900 mg twice weekly for 3 months (3RIF/INH),
- INH 300 mg daily for up to 6 years (continuous INH or CINH), and
- The control regimen INH 300 mg daily for 6 months.

Randomization ratio was 2:2:2:1 for the 3RPT/INH, 3RIF/INH, 6INH and CINH respectively. The primary endpoint was tuberculosis free survival.

HIV-infected patients with TST of 5 mm or greater were screened for enrollment from September 2002 through June 2005. Eligible patients were at least 18 years of age, were not pregnant or breast-feeding, and did not have active tuberculosis, based on symptom review and chest radiography, and, if indicated, sputum culture. Patients were also excluded if they had ever received tuberculosis therapy for more than 2 months, were currently receiving antiretroviral therapy, or had a CD4 cell count of less than 200 per cubic millimeter.

During the treatment period, scheduled visits occurred once weekly for the rifapentine isoniazid group and twice weekly for the rifampin–isoniazid group, every 2 weeks for the first 6 months for the two isoniazid groups, and monthly thereafter for the continuous-isoniazid group. Patients who had completed the assigned study regimen or had discontinued it were seen every 6 months until the end of the trial.

Patients were screened for tuberculosis symptoms at each study visit and a sputum smear, mycobacterial culture, and chest radiography were performed for those with symptoms. ALT and AST levels were measured in all patients 1, 2, and 6 months after randomization, and every 6 months thereafter in the continuous isoniazid group. Patients eligible for antiretroviral therapy were referred to an HIV clinic for the initiation of such therapy but remained in the study. Women who became pregnant while receiving rifapentine–isoniazid or rifampin–isoniazid were switched to the 6-month–isoniazid group.

The primary end point was tuberculosis-free survival. Cases were classified as confirmed, probable, or possible tuberculosis. Confirmed tuberculosis was defined as the presence of clinical signs and symptoms and a positive culture for *M. tuberculosis* from any site. Probable tuberculosis was defined as the presence of signs and symptoms with acid-fast bacilli in a sputum smear or caseous necrosis in a tissue-biopsy specimen. Possible tuberculosis was defined as the presence of signs and symptoms without microbiologic or histologic evidence of *M. tuberculosis* but with a clinical response to antituberculosis therapy. An independent end-point committee reviewed and categorized all end points.

Reference ID: 3648146

The secondary outcomes of the study were adherence to the study regimen, adverse events, discontinuation of study medication for any reason, and mycobacterial drug resistance in patients with tuberculosis. Serious adverse events were defined as grade 3 or 4 adverse events according to the Division of AIDS toxicity table, hospitalization, or death. Pregnancy also was reported as a serious adverse event but was not analyzed as such.

The trial was originally designed to show the superiority of the three new regimens for preventing tuberculosis over isoniazid for 6 months. The annual risk of tuberculosis was assumed to be 6% in the 6-month isoniazid group, rifapentine–isoniazid and rifampin–isoniazid regimens were assumed to reduce the incidence of tuberculosis by 50%, and continuous-isoniazid regimen was assumed to reduce the incidence by 82%. Type 1 error was set at 0.05, and power estimated at 90%.

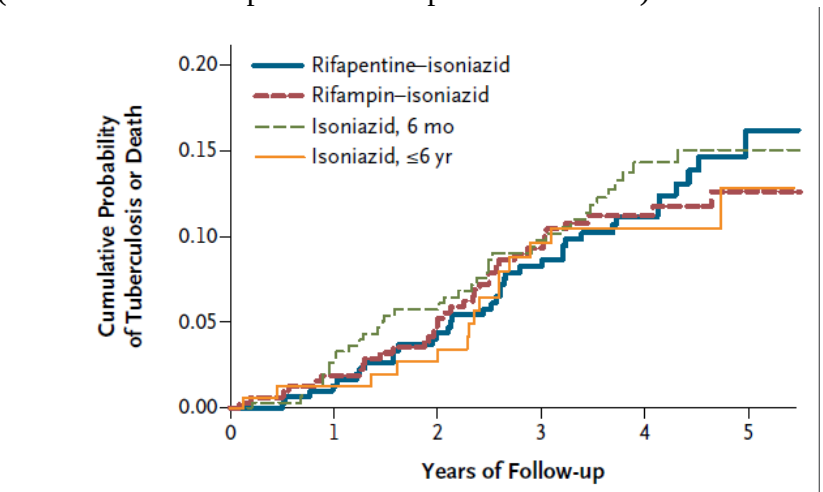
1150 subjects were randomized, 329 subjects received 3RPT/INH, 329 received 3RIF/INH, 328 received 6INH and 164 received CINH. One subject withdrew consent from each of the 3RPT/INH and 6INH groups. The following table was adapted from Tables 1, 2 and 4 in the published article.

Table 6: Subject Characteristics and Efficacy Results – Martinson Study

	3RPT/INH N = 328	**3RIF/INH N = 329**	**CINH N = 164**	**6INH N = 327**
Female	277 (84.5%)	267 (81.2%)	139 (84.8%)	273 (83.5%)
Age (Median, IQ Range)	30.3 (26-35)	30.5 (27-34)	30.2 (25-34)	30.4 (26-35)
Black	325 (99.1%)	327 (99.4%)	163 (99.4%)	327 (100%)
Median TST	14.5	15	15	15
CD4 (Median, IQ range)	471 (352-666)	498 (353-696)	476 (346-644)	490 (340-670)
Median follow up (yrs)	4.0	4.1	3.9	3.9
Took 90% of assigned dose in time allotted	95.7%	94.8%	*	83.8%
TB cases Person-years of follow up Rate per 100 person-years	24 1187.5 2.0	24 1219.7 2.0	8 561.0 1.4	22 1143.9 1.9
Deaths Person-years of follow up Rate per 100 person-years	17 1223.6 1.4	16 1269.8 1.3	8 574.2 1.4	25 1180.0 2.1
Death or TB Cases Person-years of follow up Rate per 100 person-years	37 1187.5 3.1	35 1219.7 2.9	15 561.0 2.7	41 1143.9 3.6
Culture-Confirmed TB cases	21/24	18/24	5/8	18/22

* 60.4% of patients received daily isoniazid for more than 3 years, and 43.3% for more than 4 years. The median duration of receipt of continuous isoniazid was 3.3 years (interquartile range, 2.1 to 4.3).

Figure 2: Kaplan-Meier Estimates of the risk of tuberculosis or death in ITT, according to treatment group (Martinson et al. copied from the published article).



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

At the end of the study, 887 of the 1148 patients (77.3%) had been seen in the previous 6 months or had a known date of death. Tuberculosis was diagnosed in 78 patients, of whom 62 (79%) had confirmed tuberculosis, 11 (14%) had probable tuberculosis, and 5 (6%) had possible tuberculosis. The overall incidence of all tuberculosis was 1.9 cases per 100 person-years. There were 66 deaths during the follow-up period, for an overall incidence of 1.6 deaths per 100 person-years.

There were no significant differences in the incidences of tuberculosis or death between any of the three groups treated with the newer regimens and the control group (P>0.05 for all comparisons, by the log-rank test).

The main reasons for stopping therapy were: pregnancy (34 patients), initiation of highly active antiretroviral therapy (27 patients, all in the continuous-isoniazid group), and withdrawal from the study because of work responsibilities (14 patients). A grade 3 or 4 elevation in AST or ALT occurred during the treatment phase in 1.5%, 2.4%, 28.0%, and 5.5% of patients in the rifapentine–isoniazid, rifampin–isoniazid, continuous- isoniazid, and 6-month–isoniazid groups, respectively.

Table 7: Adverse Events – Martinson Study

	3RPT/INH N = 328	3RIF/INH N = 329	CINH N = 164	6INH N = 327
Death	17 (5.2%)	16 (4.9%)	8 (4.9%)	25 (7.6%)
Grade 3 Toxicity	17 (5.2%)	15 (4.6%)	35 (21.3%)	17 (5.2%)
Grade 4 Toxicity	4 (1.2%)	9 (2.7%)	18 (11.0%)	14 (4.3%)
D/C treatment due to AE	4 (1.8%)	8 (3.8%)	50 (36.5%)	4 (1.9%)

Adapted from Table 3 in the published article

Reviewer's Comments
TB per 100 p-y was 2 in the 3RPT/INH arm and 1.9 in the 6INH arm. These rates are considerably higher than the rates in TBTC Study 26 HIV substudy (TB per 100 p-y 0.39 in the 3RPT/INH arm and 1.25 in 9INH arm). Subjects in Study 26 substudy were mainly male (70%) and approximately1/3 were white, whereas subjects in Study Martinson were predominantly female (85%) and black (99%). Median CD4 count was similar in the two studies (approximately 500 cells).The higher TB rates noted in South Africa may be due to the higher prevalence of TB, with acquisition of new infections rather than reactivation of LTBI.

This study was designed to show superiority of the 3RPT/INH regimen over the standard 6INH regimen. Superiority was not shown, but the cumulative TB rates, TB per 100 py, and cumulative TB or death rates were similar in the 3RPT/INH and 6INH and cINH arms.

The proportion of subjects who completed >90% of the assigned regimen in the allotted time was higher among 3RPT/INH recipients compared to 6INH recipients (95.7% vs. 83.8%). This finding is similar to main Study 26 and HIV substudy, where treatment completion was significantly higher among 3RPT/INH recipients compared to 9INH recipients.

5.3.5 Schechter et al. Study

Reference: Schechter M., Zajdenverg R, Falco G, Barnes G, Faulhaber JC, Coberly J, Moore R, Chaisson R. Weekly rifapentine/isoniazid or daily rifampin/pyrazinamide for latent TB in household contacts. Am J Respir Crit Care Med 2006;173:922-926

The study was conducted in Brazil. The protocol was approved by the Johns Hopkins Medicine, Federal University of Rio de Janeiro, and Brazilian Ministry of Health institutional review boards. All participants signed informed consent.

This was a randomized open label study comparing 900 mg rifapentine/isoniazid weekly for 3 months (3RPT/INH) to 450-600 mg rifampin/pyrazinamide 750-1500 mg daily for 2 months (2RIF/PZA) in preventing TB in household contacts of patients with pulmonary TB.

Subjects ≥18 years of age, with TST induration of 5 mm or more, no TB symptoms, a chest radiograph without evidence of active TB or evidence of liver or renal dysfunction or anemia and who had never received TB drugs for more than one month were eligible.

Subjects were enrolled in household clusters: the first enrolled contact of an index patient with TB was randomized to a treatment regimen, and subsequent contacts of that index case received the same treatment arm. Randomization was 1:1. PZA and RIF dosing was weight based. RPT/INH ingestion was directly observed. RIF/PZA ingestion was directly observed one dose per week and self-administered otherwise. Participants were offered HIV serology testing at baseline.

Assuming that the risk of TB to be 8% over 2 years, the efficacy of rifampin and pyrazinamide to be 90% (i.e., case rate of 0.8%) and no more than a 3.2% absolute difference in TB rates between the treatment arms, 720 participants were needed to achieve 80% power with two-tailed level of 0.05.

The study was prematurely halted after a total of 399 subjects were enrolled due to high rates of hepatotoxicity in the 2RIF/PZA arm. One subject in the 3RPT/INH arm was HIV positive.

The following table was adapted from Tables 1 and 3 and the text in the published article.

Table 8: Study Results – Schechter Study

	3RPT/INH	2RIF/PZA
N Enrolled	206	193
Mean age	37.7	37.0
Female	63 (30.5%)	56 (29.0%)
ETOH	34.5%	38%
Completed Treatment	192	181
Mean follow up	2.7 years	2.7 years
TB Cases	3 (1.46%)	1 (0.52%)
TB Rate/100 person-year	0.5	0.2
Death	1 (0.5%)	3 (1.5%)
Grade 3 hepatotoxicity*	2 (1.0%)	14 (7.3%)
Grade 4 hepatotoxicity*	0	11 (5.7%)
Either Grade 3 or 4	2 (1.0%)	20 (10.4%)¥
Pregnancy	1 (0.5%)	4 (2.1%)

*If initial Grade was 3 but subsequently 4, subject was counted in both categories. ¥ P value 0.001

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Three TB cases occurred in the 3RPT/INH arm (1.46%), versus one case in the 2RIF/PZA arm (0.52%; difference 0.94%; 95% CI 1.6, -3.7%; p 0.66). TB incidence per 100 person year was 0.5 in the 3RPT/INH arm and 0.2 in the 2RIF/PZA arm (relative risk, 2.8; 95% CI, 0.3, 26.8; p 0.66).

Grade 3 or 4 hepatotoxicity occurred in 2 of 206 (1%) in 3RPT/INH arm and 20/193 (10%) in 2RIF/PZA arm (p = 0.001). No patient had symptomatic hepatotoxicity, none were hospitalized, and all resolved within 4-12 weeks.

6 Review of Efficacy

Efficacy Summary

TBTC Main Study 26 enrolled subjects with LTBI who are at high risk for TB disease, including children and HIV infected individuals. The majority of subjects were enrolled in the United States or Canada (approximately 90%). Approximately 2.5% were HIV infected and approximately 10% were children <18 years of age. The study objective was initially designed to show the equivalence of rifapentine plus isoniazid given weekly for 3 months by directly observed therapy to self-administered isoniazid given daily for 9 months (3RPT/INH vs. 9INH) in preventing TB disease. The study was later amended to show non-inferiority of the experimental regimen to 9INH at a NI margin of 0.75%.
The NDA applicant, Sanofi, proposed a margin of 0.35%. The FDA NI margin calculation indicated that a margin of 0.091% would preserve 50% of the difference in effectiveness between 9 months of daily INH and 3 months of daily INH.

Subjects who met the inclusion criteria were randomized, and close contacts from the same household (clusters) were assigned to the same treatment arm to which the first subject was randomized. A higher proportion of 3RPT/INH subjects were enrolled as part of a cluster (23% vs 19%). The characteristics of subjects of who were randomized, subjects who were enrolled and subjects who were later found to be eligible were otherwise balanced between the two treatment arms as to age, sex, ethnicity, race, HIV, HCV or HBV infection status and history of alcohol or drug use. Although a higher proportion of 9INH subjects were excluded from the PP population, the characteristics of the PP population remained balanced between the two treatment arms.

The primary endpoint of TBTC Study 26 was the development of culture-confirmed TB in adults and culture-confirmed or clinical TB in children <18 years of age at 33 months post-enrollment in the MITT population (subjects enrolled and eligible). Twenty subjects developed culture-confirmed TB and two children developed clinical TB. Cumulative TB rates were 0.43% and 0.19% in the 9INH and 3RPT/INH arms respectively. The difference was -0.24, 95% CI interval (-0.050, 0.014). The upper bound of the 95% CI excludes 0.091; 3RPT/INH is non-inferior to

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9INH. TB rates per 100 py were 0.16 and 0.07 in the 9INH and 3RPT/INH arms respectively. Seventy-one deaths occurred during the 33 month period, 40 in the 9INH arm (one also developed TB) and 31 in the 3RPT/INH arm. The rates of composite endpoint of TB or death were 1.55% and 1.01% in the 9INH and 3RPT/INH arms respectively. The difference was -0.54%, 95% CI (0.01, 1). Additional sensitivity analysis to estimate the rates of TB among subjects lost to follow up indicated 1 additional case of TB was projected among losses to follow up in the INH arm and 0.43 additional case of TB was projected among losses to follow up in the 3RPT/INH arm. Dose response was noted in 9INH arm, but no dose response was noted in 3RPT/INH arm. In the main study, TB rates were higher in HIV-infected individuals in both treatment arms.

Secondary endpoints included culture-confirmed or clinical TB at any age, treatment adherence, treatment completion, treatment discontinuation due to a treatment related adverse event, and occurrence of Grade 3 or 4 toxicities. An additional 4 adult subjects, two in each arm, developed clinical TB. TB rates were 0.45% and 0.26% in the 9INH and 3RPT/INH arms respectively. A statistically significant higher proportion of 3RPT/INH subjects took at least 90% of doses and completed prescribed regimen in the allotted time. A statistically significantly higher proportion of 9INH subjects discontinued treatment for any reason, while a statistically higher proportion of 3RPT/INH subjects discontinued treatment due to a treatment related adverse event. The occurrence of Grade 3 and 4 toxicities were similar in the two treatment arms. The main toxicity associated with 3RPT/INH administration was hypersensitivity reaction, while the main toxicity associated with 9INH administration was hepatitis.

Because the target number of children and HIV-infected individuals was not achieved during the main TBTC Study 26, enrollment was extended for both groups. The study report for the pediatric substudy included all pediatric subjects enrolled in the main study and during the extension phase. Similarly, the study report for the HIV substudy included all HIV infected subjects enrolled in the main study and during the extension phase. Effectiveness conclusions for the primary endpoint were the same in the substudies compared to the main study. Similar to the main study, treatment adherence, treatment compliance and completion of the study regimen within the allotted time were significantly higher in the 3RPT/INH arm in the pediatric and HIV substudies.

6.1 Treatment of LTBI

Because the CDC datasets for TBTC Study 26 did not conform to CDISC standards, Sanofi contracted an independent CRO (PharmaStat) to map the raw data to CDISC SDTM and ADaM. Some events, especially in the disposition tabulation and adverse events analysis datasets, were re-classified, resulting in discrepancies between the results as reported in the converted datasets and the CSR based on the legacy datasets.

The Clinical Study Report submitted to this NDA was the same report submitted by the CDC to IND 46,954. The CSR interpretation of efficacy was based on NI margin of 0.75%.

6.1.1 Methods

In TBTC Main study 26, 11,637 patients were screened and 8053 patients were enrolled. Of the 8053 enrolled, 6364 (79%) were randomized and 1689 (21%) were enrolled in clusters.

In TBTC Study 26 pediatric substudy, 1058 subjects were enrolled, 706 in the main study and 252 during the extension phase. The reported results included all pediatric subjects enrolled within the main study and subsequent extension.

In TBTC Study 26 HIV substudy, 403 HIV infected subjects were enrolled, 212 in the main study and 181 in the extension period. The reported results included all HIV infected subjects enrolled within the main study and subsequent extension.

Please refer to the Venn diagram (Figure 1) regarding the overlapping population enrolled within the main study and the subsequent extension phases.

The main study and the substudies defined the Intent to Treat (ITT) population as all subjects who were enrolled. These included eligible subjects and subjects later found to be non-eligible, such as contacts of drug-resistant TB or culture negative source cases and young children with negative TST on initial and repeat testing.

The modified intent to treat (MITT) population included all enrolled subjects who were later found to be eligible for the study (an endpoints committee blinded to subject assignment decided if a subject met eligibility criteria).

The Per-Protocol population included all persons in the MITT population who completed the study drug within the targeted time period (11-12 doses of RPT/INH within 10-16 weeks, or 240-270 doses of INH within 35-52 weeks), or who 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.

The safety population included all enrolled subjects who received at least one dose of the study drug.

6.1.2 Subject Disposition

Table 9: Subject Disposition and Analysis Populations - TBTC Study 26 Main

	9INH	3RPT/INH
Total Enrolled (ITT)	**3908**	**4145**
Randomized	3190 (81.6%)	3174 (76.6%)
Enrolled as part of cluster	718 (19.4%)	971 (23.4%)
Not Treated - CSR	**149 (3.8%)**	**105 (2.5%)**
Incarcerated	7	0
Moved out of country	1	2
Not compliant with study drug	28	8
Withdrew consent	49	76
Pregnant	5	1
Clinician decision	5	3
Positive TST not confirmed	3	1
Source TB culture negative	5	3
Source TB INH or RIF R	43	11
TB at enrollment	3	0
Safety Population	**3759 (96.2%)**	**4040 (97.5%)**
Eligible - MITT	**3745 (95.8%)**	**3986 (96.2%)**
Not Eligible – Excluded from MITT	**163 (4.2%)**	**159 (3.8%)**
Reasons for exclusion from MITT		
Source INH or RIF R	79	82
Source negative TB culture	50	53
Positive TST not confirmed	23	14
Source case missing DST results	7	7
TB at enrollment	4	3
Completed Regimen per protocol (PP)	**2585 (66.1%)**	**3273 (79.0%)**
Excluded from PP	**1160 (29.7%)**	**713 (17.2%)**
Reasons for exclusion from PP		
Out of window for dose/duration	129	69
Died before 75% doses	2	0
Withdrew consent	66	54
AE with discontinuation	139	196
Lost to FU during treatment phase	293	60
Clinician decision	49	21
Refused treatment	225	224
Pregnant	53	20
Other/Unknown	204	69
Completed 33 months of follow up	**3174 (81.2%)**	**3475 (83.8%)**

DST = Drug susceptibility results

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Table 10: Analysis Populations - First member Randomized – TBTC Study 26 Main

	9INH	3RPT/INH
ITT	3190	3174
MITT	3074 (96.4%)	3074 (96.8%)
PP	2101 (65.9%)	2496 (78.6%)

Reviewer's Comments
The reasons for non-treatment reported in the clinical study report could not be replicated from the submitted datasets.

A similar proportion of subjects were found to be ineligible after enrollment: 4.2% in the 9INH arm and 3.8% in the 3RPT/INH arm. Reasons for ineligibility (exclusion from MITT) were balanced between the two treatment arms. The main reasons were a source patient who either had negative TB culture or had an isolate that was resistant to either INH or RIF.

A higher proportion of 3RPT/INH subjects were enrolled as part of cluster (23% vs 19%).

A statistically significant higher proportion of subjects were excluded from the PP population in the 9INH arm compared to the 3RPT/INH arm: 1160 (29.7%) and 713 (17.2%) respectively, $p<0.001$. The main reasons for the imbalance were loss to follow up, doses outside the timeframe specified and pregnancy. These reasons reflect the longer duration of INH administration compared to 3RPT/INH administration and also the fact that 3RPT/INH was given by DOT whereas INH was self-administered. A significantly higher proportion of subjects in the 3RPT/INH arm discontinued treatment due a treatment-related adverse event ($p=0.02$). This is of interest because the longer duration of INH administration biases discontinuation due to treatment related AE in favor of 3RPT/INH.

Similar to the overall population enrolled, a significantly higher proportion of randomized subjects were included in the PP population in the 3RPT/INH arm.

Only one study site, site 20 in Texas, enrolled ≥ 10% of subjects. Two other study sites, one in the US and the other in Brazil, enrolled ≥ 5% of subjects.

Table 11: Sites that Enrolled ≥5% of Subjects –TBTC Study 26 Main

		9INH	3RPT/INH
Study Site	**Country**	**ITT**	
		N = 3908	**N = 4145**
20	USA	678 (17.3%)	669 (16.1%)
29	Brazil	329 (8.4%)	336 (8.1%)
40	USA	322 (8.2%)	334 (8.1%)
MITT			
		N = 3745	**N = 3986**
20	USA	645 (17.2%)	640 (16.1%)
29	Brazil	300 (8.0%)	299 (7.5%)
40	USA	287 (7.3%)	321 (8.1%)
PP			
		N = 2585	**N = 3273**
20	USA	324 (12.5%)	526 (16.1%)
29	Brazil	230 (8.9%)	253 (7.7%)
40	USA	204 (7.9%)	257 (7.9%)

Table 12: Subject Disposition and Analysis Populations – TBTC 26 Pediatric Substudy

	9INH	3RPT/INH
Enrolled (ITT)	**506**	**552**
Randomized	419 (82.8%)	438 (79.3%)
Part of Cluster	87 (17.2%)	114 (20.7%)
MITT (Eligible)	**436 (86.2%)**	**472 (85.5%)**
Excluded from MITT	**70 (13.8%)**	**80 (14.5%)**
Positive TST not confirmed	46	45
Source TB R to INH or RIF	14	19
Source TB culture negative	8	13
Source TB missing DST	1	3
TB disease	1	0
PP	**353 (69.8%)**	**416 (75.4%)**
Excluded from PP	**83 (30.2%)**	**56 (24.6%)**
Out of window for dose/duration	28	20
Withdrew consent	5	4
Treatment related AE	3	8

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Lost to follow up	26	5
Clinician decision	7	3
Refused treatment	15	16
Safety	**493 (97.4%)**	**539 (97.6%)**
Not Treated	**13 (2.6%)**	**13 (2.4%)**
Clinician decision	0	1
Incarcerated	1	0
Positive TST not confirmed	1	4
Refused treatment	1	4
Source TB resistant to INH or RIF	8	2
TB at enrollment	1	0
Withdrew consent	0	2
Discontinued study	**63 (12.5%)**	**69 (12.5%)**
N of patient years of follow up	**1203**	**1295**

Reviewer's Comments
Similar to the main study, a higher proportion of subjects were enrolled as part of a cluster in the 3RPT/INH arm. Overall, subjects were balanced as to the reasons for MITT ineligibility, reasons not to receive treatment, and study discontinuation. A higher number of subjects were lost to follow up in the 9INH arm, likely reflecting the longer duration of treatment in that arm.

Table 13: Subject Disposition and Analysis Populations – HIV Substudy

	9INH	3RPT/INH
Enrolled (ITT)	**195**	**208**
Eligible (MITT)	**193 (99.0%)**	**206 (99.0%)**
Excluded from MITT	**2 (1.0%)**	**2 (1.0%)**
Positive TST not confirmed	1	0
Source TB culture negative	1	1
TB disease diagnosed	0	1
At least one dose (Safety)	**186 (95.4%)**	**207 (99.5%)**
Not treated	9 (4.6%)	1 (0.5%)
Completed regimen per protocol (PP)	**123 (63.1%)**	**183 (88.0%)**
Excluded from PP	**70 (36.3%)**	**23 (11.2%)**
Out of window for dose/duration	28 (14.5%)	7 (3.4%)
Withdrew consent	2 (1.0%)	0
Drug toxicity	8 (4.1%)	7 (3.4%)
Lost to FU	18 (9.3%)	8 (3.9%)
Clinician decision	7 (3.6%)	0
Refused Rx	3 (1.6%)	1 (0.5%)

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Incarcerated	4 (2.1%)	0
Discontinued treatment	**63 (32.3%)**	**24 (11.5%)**
Completed 33 month follow up	**148 (75.9%)**	**157 (75.5%)**

Reviewer's Comments
Similar to the main study and to the pediatric substudy, more 9INH recipients were lost to follow up or did not receive the prescribed number of doses during the allotted time.

6.1.3 Subject Characteristics

Table 14: Subject Characteristics – ITT Population – TBTC Study 26 Main

	9INH N = 3908	3RPT/INH N = 4145
Indication for LTBI treatment		
Close contact of TB case	2767 (70.8%)	3012 (72.7%)
Recent TST converter	977 (25.0%)	955 (23.0%)
HIV infected	74 (1.9%)	88 (2.1%)
Fibrosis on CXR	90 (2.3%)	90 (2.2%)
Age		
Mean (SD)	36 (14.7)	36.6 (14.9)
Median (Range)	35 (2-103)	36 (2-89)
Age 2-11 years	84 (2.1%)	107 (2.6%)
Age 12-17 years	267 (6.8%)	248 (6.0%)
≥18 years	3557 (91.0%)	3790 (91.4%)
Female	1812 (46.4%)	1847* (44.6%)
Male	2096 (53.6%)	2297 (55.4%)
Race		
White	2269 (58.1%)	2400 (57.9%)
Black or African American	975 (24.9%)	1002 (24.2%)
Asian/Pacific Islander	511 (13.1%)	513 (12.4%)
American Indian/Alaskan	34 (0.9%)	86 (2.1%)
Other/Unknown	119 (3.0%)	144 (3.4%)
Ethnicity		
Hispanic or Latino	1550 (39.7%)	1683 (40.6%)
Not Hispanic or Latino	2357 (60.3%)	2461 (59.4%)
Unknown	1	1
Country		
USA/Canada	3473 (88.9%)	3660 (88.3%)
Brazil/Spain	435 (11.1%)	485 (11.7%)
BMI Median	26.3	26.4
TST mm (median)	15	15

Persons enrolled in a cluster	1130 (28.9%)	1433 (34.6%)
HIV Infection		
Positive	102 (2.6%)	110 (2.6%)
Negative	1817 (46.5%)	1816 (43.8%)
Unknown	1989 (50.9%)	2219 (53.6%)
HCV Infection		
Yes	98 (2.5%)	99 (2.4%)
No	3773 (96.6%)	4003 (96.6%)
Unknown	37 (0.9%)	43 (1.0%)
HBV Infection		
Yes	60 (1.5%)	42 (1.0%)
No	3807 (97.4%)	4055 (97.8%)
Unknown	41 (1.1%)	48 (1.2%)
History of ETOH	1954 (50.0%)	1983 (47.8%)
IVDU	138 (3.5%)	151 (3.6%)

*The gender of one subject was not specified
HCV = Hepatitis C virus, HBV = Hepatitis B virus, ETOH = alcohol, IVDU = intravenous drug use – all by patient self-report

Table 15: Subject Characteristics of the Randomized Members of ITT Population – TBTC Study 26 Main

	9INH N = 3190	3RPT/INH N = 3174
Indication for treatment of LTBI		
Close contact of TB case	2054 (64.4%)	2051 (64,6%)
Recent TST converter	973 (30.5%)	947 (29.8%)
HIV infected	74 (2.3%)	88 (2.8%)
Fibrosis on CXR	89 (2.8%)	88 (2.8%)
Age		
Median (Range)	36 (2-90)	36 (2-89)
Age 2-11 years	47 (1.5%)	61 (1.9%)
Age 12-17 years	176 (5.5%)	156 (4.9%)
≥18 years	2967 (93.0%)	2957 (93.2%)
Female	1468 (46.0%)	1465 (46.2%)
Male	1722 (54.0%)	1708 (53.8%)
Race		
White	1784 (55.9%)	1803 (56.8%)
Black or African American	864 (27.1%)	840 (26.5%)
Asian/Pacific Islander	412 (12.9%)	388 (12.2%)
American Indian/Alaskan	31 (1.0%)	39 (1.2%)
Other/Unknown	99 (3.1%)	104 (3.3%)

Ethnicity		
Hispanic or Latino	1163 (36.5%)	1182 (37.2%)
Not Hispanic or Latino	2026 (63.5%)	1991 (62.7%)
Country		
USA/Canada	2890 (90.6%)	2836 (89.4%)
Brazil/Spain	300 (9.4%)	338 (10.6%)
BMI Median	26	27
TST mm (median)	15	15
Persons enrolled in a cluster	412 (12.9%)	462 (14.6%)
HIV Infection	102 (3.2%)	104 (3.3%)
HCV Infection	94 (2.9%)	86 (2.7%)
HBV Infection	52 (1.6%)	32 (1.0%)
History of ETOH	1674 (52.5%)	1618 (51.0%)
IVDU	135 (4.2%)	131 (4.1%)

Table 16: Subject Characteristics – MITT – TBTC Study 26 Main

	9INH N = 3745	**3RPT/INH N = 3986**
Indication for treatment of LTBI		
Close contact of TB case	2609 (69.7%)	2857 (73.3%)
Recent TST converter	972 (26.0%)	953 (23.9%)
HIV infected	74 (2.0%)	87 (2.2%)
Fibrosis on CXR	90 (2.4%)	89 (2.3%)
Age		
Mean (SD)	36.1 (14.5)	36.8 (14.7)
Median (Range)	35 (2-103)	36 (2-89)
Age 2-11 years	61 (1.6%)	87 (2.2%)
Age 12-17 years	254 (6.8%)	235 (5.9%)
≥18 years	3430 (91.6%)	3664 (91.9%)
Female	1741 (46.5%)	1775* (44.5%)
Male	2004 (55.5%)	2210 (55.4%)
Race		
White	2160 (57.7%)	2296 (57.6%)
Black or African American	947 (25.3%)	978 (24.5%)
Asian/Pacific Islander	490 (13.1%)	494 (12.4%)
American Indian/Alaska	33 (0.9%)	84 (2.1%)
Other/Unknown	115 (3.1%)	134 (3.3%)
Ethnicity		
Hispanic or Latino	1470 (39.3%)	1609 (40.4%)

Not Hispanic	2275 (60.7%)	2377(59.6%)
Country		
USA/Canada	3341 (88.9%)	3542 (89.2%)
Brazil/Spain	404 (11.1%)	444 (11.4%)
BMI (Median)	26.3	26.5
TST mm (Median)	15	15
Part of cluster	1050 (28.0%)	1345 (33.7%)
HIV Infection		
Positive	100 (2.7%)	109 (2.7%)
Negative	1761 (47.0%)	1750 (43.9%)
Unknown	1884 (50.3%)	2127 (53.4%)
HCV Infection		
Yes	97 (2.6%)	99 (2.5%)
No	3613 (96.5%)	3845 (96.5%)
Unknown	35 (0.9%)	42 (1.0%)
HBV Infection		
Yes	60 (1.6%)	42 (1.0%)
No	3646 (97.4%)	3897 (97.8%)
Unknown	39 (1.0%)	47 (1.2%)
History of ETOH	1888 (50.4%)	1929 (49.5%)
IVDU	136 (3.6%)	149 (3.7%)

*The gender of one subject was not specified

Table 17: Subject Characteristics – PP – TBTC Study 26 Main

	9INH N = 2585	**3RPT/INH N = 3273**
Indication for treatment of LTBI		
Close contact of TB case	1782 (68.9%)	2368 (72.3%)
Recent TST converter	683 (26.4%)	761 (23.3%)
HIV infected	50 (1.9%)	77 (2.4%)
Fibrosis on CXR	70 (2.7%)	67 (2.0%)
Age		
Mean (SD)	36.1 (14.7)	36.4 (14.7)
Median (Range)	35 (4-103)	35 (4-89)
Age 2-11	53 (2.1%)	77 (2.4%)
Age 12-17	203 (7.8%)	208 (6.4%)
≥18	2329 (90.1%)	2988 (91.3%)
Female	1206 (46.6%)	1427 (43.6%)
Male	1379 (53.4%)	1846 (56.4%)

Race		
White	1479 (57.2%)	1876 (57.3%)
Black or African American	640 (24.8%)	815 (24.9%)
Asian/Pacific Islander	367 (14.2%)	405 (12.4%)
North American Indian/Alaskan	18 (0.7%)	61 (1.9%)
Other/Unknown	81 (3.1%)	116 (3.5%)
Ethnicity		
Hispanic	1010 (39.1%)	1357 (41.5%)
Not Hispanic	1575 (60.0%)	1916 (58.5%)
Country		
USA/Canada	2282 (88.3%)	2885 (88.1%)
Brazil/Spain	303 (11.7%)	388 (11.9%)
BMI (median)	26	27
TST mm (median)	15	15
Persons enrolled in a cluster	745 (28.8%)	1155 (35.3%)
HIV Infection		
Positive	65 (2.5%)	91 (2.8%)
Negative	1331 (51.5%)	1395 (42.6%)
Unknown	1189 (46.0%)	1787 (54.6%)
HCV Infection		
Yes	52 (2.0%)	31 (0.9%)
No	2511 (97.1%)	3168 (96.8%)
Unknown	22 (0.9%)	74 (2.3%)
HBV Infection		
Yes	35 (1.3%)	34 (1.0%)
No	2526 (97.7%)	3204 (97.9%)
Unknown	24 (1.0%)	35 (1.1%)
History of ETOH	1215 (47.0%)	1548 (47.3%)
IVDU	85 (3.3%)	105 (3.2%)

Reviewer's Comments
The ITT and MITT populations were balanced as to reason for enrollment, age, sex, race, ethnicity, country of enrollment, self-reported hepatitis B and C status and alcohol and IV drug use. Approximately 2.5 to 3% were HIV infected and HIV status was unknown in approximately 50% in each arm. A higher proportion of subjects were enrolled as part of a cluster in the 3RPT/INH arm but the characteristics of the randomized subjects remained balanced.

A higher proportion of patients were excluded from the PP population in the 9INH arm compared to the 3RPT/INH arm, but the characteristics of subjects remained balanced between the two treatment arms.

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Table 18: Subject Characteristics – MITT – Pediatric Substudy

	9INH N = 436	3RPT/INH N = 472
Indication for LTBI Rx		
Recent TST converter	36 (8.2%)	33 (7.0%)
Close contact	399 (91.6%)	437 (92.6%)
HIV infected	1 (0.2%)	2 (0.4%)
Age (Median, Range)	13 (2-17)	12 (2-17)
2-4 years	78 (18.0%)	114 (24.2%)
5-11 years	102 (23.4%)	121 (25.6%)
12-17 years	256 (58.7%)	237 (50.2%)
Male	201 (46.1%)	258 (54.7%)
Female	235 (53.9%)	214 (45.3%)
White	298 (68.3%)	341 (72.2%)
Black	70 (16.1%)	67 (14.2%)
Asian/Pacific Islander	49 (1.1%)	35 (7.4%)
North American Indian/Other	19 (4.4%)	29 (6.1%)
Hispanic	268 (61.5%)	319 (67.6%)
Non-Hispanic	168 (38.5%)	153 (32.4%)
USA/Canada	368 (84.4%)	386 (81.8%)
Brazil/Spain/Hong Kong	68 (15.6%)	86 (19.2%)
TST (Median) mm	15	15
HIV positive	1 (0.2%)	3 (0.6%)
HIV negative	101 (23.2%)	77 (16.3%)
HIV unknown	334 (76.6%)	392 (83.1%)
Enrolled in Cluster	191 (43.8%)	248 (52.5%)
HBV infected	1 (0.2%)	0
HBV negative	430 (98.6%)	457 (96.8%)
HBV unknown	5 (1.2%)	15 (3.2%)
HCV infected	0	0
HCV negative	431 (98.8%)	457 (96.8%)
HCV unknown	5 (1.2%)	15 (3.2%)

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Table 19: Subject Characteristics – Safety Population – Pediatric Substudy

	9INH N = 493	3RPT/INH N = 539
Age (Median, Range)	12 (2-17)	10 (2-17)
2-4 years	104 (21.1%)	163 (30.2%)
5-11 years	106 (21.5%)	129 (24.0%)
12-17 years	263 (53.4%)	247 (45.8%)
Male	232 (47.1%)	293 (54.4%)
Female	261 (52.9%)	246 (45.6%)
White	339 (68.8%)	393 (72.9%)
Black	77 (15.6%)	72 (13.4%)
Asian/Pacific Islander	55 (11.2%)	41 (7.6%)
North American Indian/Other	22 (4.5%)	33 (6.1%)
Hispanic	310 (62.9%)	369 (68.5%)
Non-Hispanic	183 (37.1%)	170 (31.5%)
USA/Canada	442 (89.7%)	480 (89.1%)
Brazil/Spain/Hong Kong	51 (10.3%)	59 (11.9%)
HIV positive	1 (0.2%)	4 (0.8%)
HIV negative	103 (20.9%)	88 (16.3%)
HIV unknown	389 (78.9%)	447 (82.9%)
HBV infected	1 (0.2%)	0
HBV negative	6 (1.2%)	524 (97.2%)
HBV unknown	486 (98.6%)	15 (2.8%)
HCV infected	0	0
HCV negative	487 (98.8%)	524 (97.2%)
HCV unknown	6 (1.2%)	15 (2.8%)

Reviewer's Comments
Statistically significantly more adolescents aged 12-17 years were enrolled in the 9INH treatment arm (53.0%) than in the 3RPT/INH treatment arm (45.5%; p=0.016), and more females were enrolled in the 3RPT/INH arm. The ITT and MITT and safety population otherwise were balanced as to reason for enrollment, HIV, HBV and HCV status, race and country of enrollment.

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Table 20: Subject Characteristics – HIV Substudy - MITT

	9INH N = 193	3RPT/INH N = 206
Indication for LTBI Rx		
Close contact of TB case	186 (96.4%)	195 (94.7%)
Recent TST converter	6 (2.6%)	11 (5.3%)
Age (median)	36 (15-71	36 (15-71)
Male	131 (67.9%)	146 (70.8%)
Race		
White	73 (37.8%)	76 (36.9%)
Black	75 (38.9%)	75 (36.4%)
Asian/Pacific Islander	3 (1.6%)	6 (2.9%)
North American Indian	4 (2.1%)	5 (2.4%)
Other	38 (19.7%)	44 (21.4%)
Hispanic	60 (31.1%)	77 (37.4%)
Not Hispanic	133 (68.9%)	128 (62.1%)
US/Canada	158 (81.9%)	157 (76.2%)
Other	35 (18.1%)	49 (23.8%)
TST median	15	15
CD4	N =160	N =176
Median, Range	537 (9-1406)	497 (55-1988)
HBV infected	19 (9.8%)	11 (5.3%)
HBV negative	169 (87.6%)	190 (92.2%)
Unknown	5 (2.6%)	5 (2.4%)
HCV infected	26 (13.5%)	22 (10.7%)
HCV negative	160 (82.9%)	181 (87.9%)
Unknown	7 (3.6%)	3 (1.5%)

Table 21: Subject Characteristics – Safety Population – HIV Substudy

	9INH N = 186	3RPT/INH N = 207
Indication for LTBI Rx		
Close contact of TB case	181 (97.3%)	196 (94.7%)
Recent TST converter	5 (2.7%)	11 (5.3%)
Age (median)	36	36
Male	126 (67.7%)	147 (71.0%)
Race		
White	70 (37.6%)	77 (37.2%)
Black	72 (38.7%)	75 (36.2%)
Asian/Pacific Islander	3 (1.6%)	6 (2.9%)

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North American Indian Multiracial	3 (1.6%) 38 (20.4%)	5 (2.4%) 44 (21.3%)
Hispanic Non-Hispanic	60 (32.2%) 126 (67.8%)	78 (37.7%) 129 (62.3%)
US/Canada Other	156 (83.9%) 30 (16.1%)	158 (76.3%) 49 (23.7%)
TST Median	15	15
CD4 count Median, Range	N = 154 541 (9-1406)	N = 176 495 (55-1988)
HBV infected HBV negative Unknown	18 (9.7%) 163 (87.6%) 5 (2.7%)	11 (5.3%) 191 (92.3%) 5 (2.4%)
HCV infected HCV negative Unknown	23 (12.4%) 156 (83.9%) 7 (3.7%)	21 (10.1%) 183 (88.4%) 3 (1.5%)

Reviewer's Comments
A higher proportion of subjects in the 9INH arm were HBV and HCV co-infected. Median CD4 count was higher in the 9INH arm (difference approximately 45 cells), The two treatment arms were otherwise matched.

6.1.4 Analysis of Primary Endpoint

The primary efficacy endpoint was the development of culture-confirmed tuberculosis in subjects ≥ 18 years old or culture-confirmed or probable (clinical) tuberculosis in subjects < 18 years old within 33 months of study enrollment.

Culture-confirmed TB was defined as a positive culture for *M. tuberculosis* from any body fluid or tissue.

Probable (clinical) TB was defined as

- Objective evidence of TB by history or physical exam *PLUS*
- Radiograph, CT or other diagnostic tests, and without concurrent illness that would explain the findings (in children < 18 years old with a positive TST, hilar adenopathy on CXR was considered evidence of TB) *PLUS*
- Either a clinical response of signs and symptoms to anti-TB therapy and objective improvement of radiologic or other diagnostic findings, or evidence of granuloma with positive stains for AFB, or caseating granulomas at autopsy or biopsy.

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A Clinical Events Committee composed of 3 reviewers external to the CDC and blinded to treatment assignment adjudicated all cases.

In the Main Study, twenty subjects had culture-confirmed TB, 19 adults and one child. An additional two cases of clinical TB occurred in children. These 22 cases were analyzed for the primary efficacy endpoint. An additional 4 cases of clinical TB occurred in adults. These cases were included in the analysis of the secondary endpoint of culture-confirmed or clinical TB occurring at any age.

Table 22: Primary Efficacy –MITT 33 Months after Enrollment – TBTC Study 26 Main

	9INH N = 3745	3RPT/INH N = 3986	Difference (95% CI)
TB Cases	15 (0.40%)	7 (0.18%)	-0.22% (-0.05, 0.02)
TB per 100 person-year	0.16	0.07	-
Cumulative TB rate	0.43%	0.19%	-0.24 (-0.051, 0.014)

Reviewer's comments
The upper bound of the 95% CI for the difference in TB cumulative rate and the upper bound of the 95% CI for the absolute TB rate exclude the NI margin of 0.091%. 3RPT/INH is non-inferior to 9INH as defined. The CI interval includes zero. Superiority is not demonstrated.

The submitted data indicated that 32 cases of culture-confirmed or clinical TB were suspected by the investigator and referred to the adjudication committee. Twenty-two of the 32 cases were included in the primary analysis: 19 cases were culture-confirmed in adults, one case was culture-confirmed in a child, and 2 cases were clinical TB in children. Narratives for these 22 cases were provided in the submission and were reviewed. I agree with the assessments regarding clinical TB in the two children.

An additional four cases were adjudicated as clinical TB in adults based on clinical and radiologic features and response to anti-TB therapy. The narratives for these 4 cases were reviewed. All had multiple specimens that were negative for AFB smear and culture, but the clinical and radiologic features were highly suspicious for/compatible with TB. These 4 cases were included in the analysis of the secondary endpoint of TB at any age.

The remaining six cases that were considered by the investigator as TB but adjudicated otherwise included four subjects in the 3RPT/INH arm (Subjects 1353, 7518, 2356 and 4950) and 2 subjects in the 9INH arm (Subjects 6375 and 2270). One subject in each arm (Subjects 2270 and 7518), the acid fast bacillus was identified as M. avium. Narratives and case report forms for the other 4 subjects were provided upon request.

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Subject 1353 was a 34 year old HIV negative Hispanic male who started 3RPT/INH treatment on 1/14/2003 and finished on 4/29/2003. He was (b) (4) *and while still* (b) (4) *complained of abdominal pain and shortness of breath. Evaluation revealed a right pleural effusion and ascites with adenopathy. Lymph node biopsy showed caseating granulomas and peritoneal fluid grew M. tuberculosis on solid and liquid media in July 2008. The isolate was sensitive to INH/RIF/EMB. This case was not counted in the primary endpoint because onset of TB was more than 5 years after enrollment, beyond the 33 months cut-off.*

Subject 2356 was a 32 year old HIV negative man who completed 3RPT/INH therapy without missing any dose on 3/2/2004. He developed cough and hemoptysis on 6/21/2005 with 18 lb. weight loss documented 3 months later. CXR was normal and only one of 10 smears was reported positive for AFB. TB cultures were negative. He was treated with levofloxacin for 2 weeks with resolution of symptoms but also given RIPE therapy (rifampin, isoniazid, pyrazinamide and ethambutol) for 2 months. He had no symptom relapse on follow up.

Subject 6375 was a 52 year old HIV and HCV infected black man who was in a rehab facility receiving multiple antibiotics (vancomycin, ceftriaxone and clindamycin – reasons for the antibacterial therapies were not stated). He completed 6 weeks of INH which was discontinued due to elevated liver enzymes. Four months later, he started to have weight loss and CT of chest revealed subcarinal adenopathy 8 months later. He was started on RIF/EMB, INH and moxifloxacin. Multiple sputum samples and BAL samples were negative for TB. He also developed neck pain with a cervical spine abscess that was not typical for TB spondylitis. He finished a one year course of TB treatment with symptomatic improvement of the neck pain.

Subject 4950 was a 64 year old HIV negative black man who finished 12 doses of 3RPT/INH. He was hospitalized 12 months later with CHF exacerbation. Sputum was negative for M. tuberculosis and he never received TB therapy.

I agree with the assessment that Subjects 6375 and 4950 did not have clinical TB. Subject 2356 had clinical symptoms that were compatible with TB and received 2 weeks of 5 drugs with TB activity (RIPE and levofloxacin) and an additional 6 weeks of 4 drug therapy. However, because this is not culture confirmed TB in an adult, the primary endpoint assessment is not impacted.

The TB cumulative rate in the 9INH arm in this trial was 0.43%. This is lower than assumed in the sample size calculations but similar to the rates reported in the IUAT trial and the compiled 11 trials analyzed in the Cochrane Collaboration Review (see NI margin calculation under section 5).

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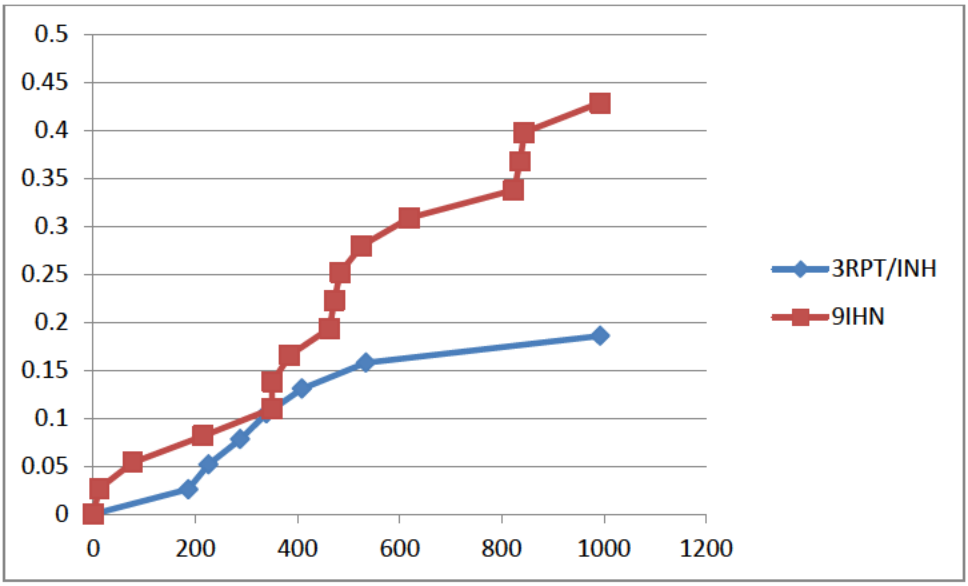
Figure 3: Cumulative TB Rates – MITT at 33 months – TBTC Study 26 Main study



Reviewer's Comments
TB disease occurrence was noted later and seemed to plateau after day 600 in the 3RPT/INH arm but continued to increase throughout the follow up period in the 9INH arm. The reasons for the later occurrence and for the plateau are unclear.

Table 23: Primary Efficacy – PP population - TBTC Study 26 Main Study

	9INH N = 2585	3RPT/INH N = 3273	Difference 95% CI
TB Cases	8 (0.31%)	4 (0.12%)	-0.19% (-0.50, 0.06)
TB per 100 person-years	0.11	0.05	-
Cumulative TB rate	0.32%	0.13%	-0.19%

Sensitivity Analyses
Analysis 1 –Removing clinical TB cases in children in 9INH arm
The two clinical TB cases in the 9INH arm were in children and occurred a year after dosing was completed. Subject 1353 in the 3RPT/INH arm had culture confirmed TB after the 33 months cut-off. If we conservatively decrease the number of cases in the 9INH arm by removing the 2 pediatric clinical cases from the primary analysis and increase the number of culture-confirmed cases in the 3RPT/INH arm by adding subject 1353, absolute TB rates are 13/3745 (0.35%) vs. 8/3986 (0.2%). The CI for the difference is (-0.41, 0.1)

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Analysis 2 - Using composite endpoint of TB or death
At 33 months, 40 deaths occurred in the INH and 31 in the 3RPT/INH arms. One of the deaths in the 9INH had culture-confirmed TB. Combining deaths and TB, 54 events occurred in the 9INH arm (1.44%) and 38 in the 3RPT/INH arm (0.95%). The 95% CI for the difference was (-0.98, 0.00001) and unadjusted p value was 0.048. The MITT composite cumulative rates in the 9INH arm and 3RPT/INH arm are 1.55% and 1.01% respectively (difference -0.54, 95% CI (-1.01, 0.03).

Table 24: Composite Endpoint of TB or death – MITT – Study 26 Main Study

	9INH N = 3745	3RPT/INH N = 3986	Difference (95% CI)
TB or death	54	38	
Composite Cumulative Rate	1.55%	1.01%	-0.54 (-1.01, 0.03)

Analysis 3 - Estimating potential TB cases from losses to follow up
The sponsor provided this analysis. The protocol defined lost to follow up as subjects with unknown outcome at 33 months after enrollment and who were not known to have died or developed TB disease from National records. A total of 990 subjects, 517 (13.8%) in the 9INH arm and 473 (11.9%) in the 3RPT/INH arm were lost to follow up.

Three methods were used to estimate the potential TB cases that may have occurred among these subjects.

The first method assumed constant TB rates for all participants throughout the entire 33 months study period for each of the treatment arms. The observation time for the 7731 subjects who were followed up and for the 990 subjects who were not followed up was calculated. The difference was the missing observation time. Using the TB event rate, the calculated missing TB cases was 1.03 (SE 1.02) for the 9INH arm and 0.43 (SE 0.65) for the 3RPT/INH arm.

Table 25: Estimation of Potential Missing TB Cases among Subjects Lost to Follow Up – TBTC 26 - Main Study

	Observed Days	TB cases	Observed Days per TB case	Lost to FU	Observed Days for LFU	Missing Days for LFU	Projected TB cases (SE)
9INH	3,460,046	15	230,670	517	275,811	238,087	1.03 (1.02)
3RPT/INH	3,717,635	7	531,091	473	243,746	226,416	0.43 (0.65)

The second method assumed that the hazard of getting TB varied over the 33 month period. This method estimated 1.17 missing TB cases in 9INH arm (SE 1.08) and 0.47 cases in 3RPT/INH arm (SE 0.69).

The third method assumed that lost to follow up participants may be different from other participants in terms of TB occurrence. Smoking was identified as the risk factor associated with TB occurrence in Study 26, and a propensity score was calculated. This method estimated 0.81 TB cases among smokers and 0.42 cases among non-smokers in the 9INH arm (total missing cases 1.23), and 0.47 TB cases among smokers and 0.07 cases among non-smokers in the 3RPT/INH arm (total missing cases 0.54). The difference in the total missing cases was -0.69.

Reviewer's Comments
Sensitivity analyses confirm the initial study findings.

In the pediatric substudy, one culture-confirmed TB case and two clinical TB cases occurred, all in subjects enrolled in the main Study, and all in 9INH recipients enrolled in the US/Canada. The culture-confirmed TB occurred in a 14 year old female with unknown HIV status who took 64 INH doses. The isolate was INH resistant. The clinical TB cases occurred in 2 year old and 5 year old male cousins who took the full 270 doses but were re-exposed to a household member with active TB. Clinical TB was diagnosed on Study days 839 and 818 respectively.

Table 26: Culture-Confirmed or Clinical TB - MITT – Pediatric Substudy

	9INH N = 436	3RPT/INH N = 472	Difference 95% CI
TB cases	3 (0.7%)	0	-0.7 (-2, 0.24)
TB Rate per 100 p-yr	0.27	0	-
Cumulative TB rate	0.78%	0	-0.78%

In the PP population, cumulative TB rate in the 9INH arm was 0.93% and the rate per 100 p-y was 0.33.

In the HIV substudy, eight culture-confirmed TB cases occurred, four in subjects enrolled in the main study (2 subjects in each arm) and four enrolled in the extension period (all 4 in the 9INH arm).

Table 27: Culture-Confirmed TB – MITT and PP - HIV Substudy

	9INH	3RPT/INH	
MITT			
	N = 193	N = 206	Difference (95% CI)
TB Cases	6 (3.1%)	2 (2.1%)	-1.0 (-5.71, 0.87)
TB per 100 person-year	1.25	0.39	-

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Cumulative TB rate	3.5%	1.01%	-2.49%
PP			
	N = 123	**N = 183**	
TB Cases	2 (0.8%)	1 (0.55%)	-0.27 (-3.94, 2.31)
TB per 100 person-year	0.63	0.21	-
Cumulative TB rate	1.81%	0.56%	-1.25

One additional case of clinical TB occurred in the 9INH arm. This case was included in the secondary outcome. This subject was also enrolled in the main study.

Reviewer's Comments
As expected, TB rates were higher in HIV infected patients compared to the overall population enrolled in the main study.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints in the main study were development of culture-confirmed or clinical TB in any age group within 33 months of enrollment, completion of the prescribed regimen, discontinuation of study treatment for any reason, discontinuation of study treatment due to a treatment related adverse drug reaction, treatment adherence, and grade 3 or 4 drug-related toxicity.

A. Development of culture-confirmed or clinical TB at any age

Twenty six cases of clinical or culture confirmed TB occurred in the MITT population in the main study, 17 in the 9INH arm and 9 in the 3RPT/INH arm.

Table 28: Culture-Confirmed or Clinical TB at Any Age – MITT and PP – Study 26 Main Study

	9INH	**3RPT/INH**	**Difference (95% CI)**
MITT			
	N = 3745	**N = 3986**	
TB Cases	17 (0.45%)	9 (0.22%)	-0.23% (-0.52, 0.04)
PP			
	N = 2585	**N = 3274**	
TB Cases	9 (0.35%)	5 (0.15%)	-0.20% (-0.52, 0.07)

B. Treatment Adherence, completion and discontinuations due to treatment-related adverse reaction

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76.5% of subjects in the 9INH arm took at least 90% of the doses prescribed compared to 85% of subjects in the 3RPT/INH arm. Approximately 5% of subjects in each arm received <10% of the prescribed doses. Subjects were considered to have completed therapy if they received at least 11 RPT doses during 16 week period or at least 240 doses INH during 52 week period.

Table 29: Treatment Adherence, Completion and Discontinuations due to Treatment-Related Adverse Reaction – MITT - Study 26 Main Study

	9INH N = 3745	3RPT/INH N = 3986	P value
Took ≥90% of doses	2866 (76.5%)	3386 (85.0%)	<0.0001
Drug Discontinued due to Treatment Related AE	139 (3.7%)	196 (4.9%)	0.02
Drug Discontinued for any reason	1160 (31%)	713 (17.9%)	<0.001
Completion of Prescribed Regimen	2585 (69%)	3273 (82.1%)	<0.0001

Reviewer's Comments
A statistically significant higher proportion of 3RPT/INH recipient completed the prescribed regimen. The finding that a significantly higher proportion of subjects adhered to treatment and completed treatment in the 3RPT/INH arm confirms the expectation that administration by DOT improves compliance with therapy.

Treatment discontinuation for any reason included losses to follow up, which occurred more frequently in the 9INH arm. It is likely that the longer treatment duration contributed to the higher incidence of treatment discontinuation for any reason in the 9INH arm.

A treatment-emergent adverse event was defined as an AE that occurred during therapy or within 60 days after last dose of study drug. Relationship to treatment was determined by the investigator, and considered in relationship to the entire regimen for subjects in the 3RPT/INH arm rather than the individual components of the combination.
A statistically significantly higher proportion of subjects discontinued treatment due to an AE that was judged to be treatment related in the 3RPT/INH arm in the MITT population. The same was true in the safety population; 142/3759 (3.8%) discontinued treatment due to TETRAE in 9INH arm vs 196/4040 (4.9%) in 3RPT/INH arm. This is an interesting finding, because the longer duration of therapy in the 9INH arm biases the safety results in favor of 3RPT/INH. However, despite the higher rate of treatment discontinuation due to an AE in the 3RPT/INH arm, more subjects in that arm completed therapy as prescribed, likely due to DOT administration and shorter treatment duration.

C. Grade 3 or 4 Toxicities
Grading of AE severity was reported using NCI CTC v.2.0 grading (see Safety Evaluation).

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Table 30: Treatment Emergent, Treatment-Related Grade 3, 4 or 5 Toxicities - TBTC 26 Main Study

	9INH N = 3759	3RPT/INH N = 4040	P value
Grade 3	84 (2.2%)	107 (2.6%)	0.23
Grade 4	13 (0.4%)	17 (0.4%)	0.70
Grade 5	0	0	

Reviewer's Comments
Treatment related Grade 3 or 4 toxicities occurred in similar proportions of subjects in each arm. However, although the rate of G3 and 4 treatment related toxicities were similar, subjects in the 3RPT/INH arm were more likely to discontinue therapy due to treatment related AE. It is possible that the different nature of the encountered toxicities in each arm encountered had an impact on the investigator's decision to discontinue treatment; toxicity leading to discontinuation in the 3RPT/INH arm mainly pertained to hypersensitivity reactions which present with clinical symptoms and appear soon after drug ingestion whereas the toxicity leading to discontinuation in the 9INH arm mainly pertained to hepatitis which may be biochemical and asymptomatic and only detected when labs are drawn at monthly intervals (See Safety Evaluation Section).

The proportion of Grade 3 and 4 toxicities was also similar for any treatment emergent AE regardless of attributed relatedness to treatment. More patients died during therapy and 60 days post therapy in the 9INH arm, reflecting the longer treatment duration in that arm.

Table 31: Treatment Emergent Grade 3, 4 or 5 Toxicities – TBTC 26 Main Study

	9INH N = 3759	3RPT/INH N = 4040	P value
Grade 3	197 (5.2%)	189 (4.7%)	0.25
Grade 4	43 (1.1%)	36 (0.9%)	0.26
Grade 5	7 (0.2%)	4 (0.1%)	0.48

Similar to the main Study, a statistically higher proportion of 3RPT/INH subjects completed treatment as prescribed in the pediatric and HIV substudies.

Table 32: Treatment Adherence, Completion, and Discontinuation – Pediatric Substudy

	9INH N = 436	3RPT/INH N = 472	P Value
Took ≥90% doses	382 (87.6%)	435 (92.1%)	0.023
Completed treatment as prescribed	353 (81.0%)	416 (88.1%)	0.003
D/C treatment for any reason	83 (19.0%)	56 (11.9%)	0.003
D/C treatment due to treatment related AE	2 (0.5%)	8 (1.7%)	-

Table 33: Treatment Adherence, Completion and Discontinuation– HIV Substudy

	9INH N = 193	3RPT/INH N = 206	P value
Completed ≥90% doses	153 (79.3%)	190 (92.2%)	0.0001
Completed regimen per protocol	123 (63.7%)	183 (88.8%)	<0.0001
D/C treatment for any reason	63 (32.6%)	24 (11.6%)	<0.0001
D/C treatment due to treatment related AE	8 (4.1%)	7 (3.4%)	0.69

6.1.6 Other Endpoints

Resistance among TB isolates in patients who developed culture positive TB

Twenty (20) subjects had positive cultures in the main study, 13 in the 9INH arm and 7 in the 3RPT/INH arm. Two subjects in the INH arm (2/13, 15%) developed TB due to INH mono-resistant TB and one subject (7.5%) had a streptomycin R isolate. One subject in the 3RPT/INH (1/7, 14%) had *M. bovis* (considered culture-confirmed TB) that was resistant to rifamycins and pyrazinamide.

One additional isolate in the 9INH arm of the HIV study was reported resistant to INH, rifampin and streptomycin in a patient from Peru.

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6.1.7 Subpopulations

Table 34: Primary Efficacy by Age, Sex, Ethnicity, Country of Enrollment, and HIV Status - MITT Main Study

	9INH N = 3745	3RPT/INH N = 3986
Age Group		
≥18 years	13/3430 (0.38%)	7/3664 (0.19%)
12-17	0/254	0/235
2-11	2/61 (3.2%)	0/87
Sex		
Females	6/1741 (0.35%)	2/1775 (0.11%)
Males	9/2004 (0.45%)	5/2210 (0.23%)
Race		
White	8/2160 (0.37%)	4/2296 (0.17%)
Black	5/947 (0.5%)	3/978 (0.3%)
Asian	0/490	0/494
American Indian	1/33 (3.0%)	0/84
Other/Unknown	1/115 (0.9%)	0/134
Ethnicity		
Hispanic	5/1470 (0.34%)	4/1609 (0.25%)
Not Hispanic	10/2275 (0.44%)	3/2378 (0.13%)
Country Group		
US/Canada	12/3341 (0.36%)	7/3542 (0.20%)
Brazil	3/404 (0.74%)	0/444
HIV Status		
HIV Positive	2/100 (2.0%)	2/109 (1.8%)
HIV negative	8/1761 (0.45%)	3/1750 (0.17%)
Unknown	5/1884 (0.3%)	1/2127 (0.05%)
Study Site		
13	1/175 (0.6%)	1/169 (0.6%)
20	3/645 (0.5%)	0/640
21	1/39 (2.6%)	0/49
22	1/161 (0.6%)	1/170 (0.6%)
24	1/138 (0.7%)	0/150 (0%)
26	0/96 (0%)	1/155 (0.6%)
28	1/116 (0.9%)	0/98 (0%)
29	2/300 (0.7%)	0/299 (0%)
31	1/104 (1%)	0/145 (0%)
40	0/287	1/321 (0.3%)
58	1/287 (0.3%)	0/55

61 63 70	1/40 (2.5%) 2/183 (1.1%) 0/59	0/30 2/189 (1.1%) 1/69 (1.5%)
Indication for treatment of LTBI		
Close contact of TB case Recent TST converter Fibrosis on CXR	13/2609 (0.5%) 1/972 (0.1%) 0/90	5/2857 (0.18%) 1/953 (0.1%) 0/87
Doses Taken		
<25% (<68 doses) 25-<50% (69-134) 50-75% (135-203) ≥75% (≥204)	5/422 (1.2%) 1/221 (0.5%) 2/205 (1.0%) 7/2897 (0.2%)	
<25% (<3 doses) 25-<50% (3-5) 50-75% (6-8) ≥75% (≥9)		0/248 1/219 (0.5%) 1/109 (0.9%) 5/3410 (0.1%)

Absolute rates rather than cumulative rates are reported

Table 35: Characteristics of Subjects with Culture Confirmed TB – HIV Substudy

	9INH N = 193	**3RPT/INH N = 206**
≥18 years	6/192 (3.1%)	2/203 (1.0%)
Male Female	5/131 (2.3%) 1/62 (1.6%)	2/146 (1.4%) 0/60
US/Canada Other	1/158 (0.6%) 5/35 (14.3%)*	2/157 (1.3%) 0/49
<25% (<68 doses) 25-<50% (69-134) 50-75% (135-203) ≥75% (≥204)	1/23 (4.3%) 1/10 (10.0%) 1/6 (16.7%) 3/154 (2.0%)	
<25% (<3 doses) 25-<50% (3-5) 50-75% (6-8) ≥75% (≥9)		0/3 0/6 0/9 2/188 (1.0%)

Absolute, not cumulative, rates
*3 in Peru, 1 in Spain, 1 in Brazil

Reviewer's Comments
As expected, TB incidence was higher among HIV infected patients compared to the overall population in the main study. Effectiveness in the HIV subpopulation enrolled in the main study was similar between the two treatment arms, but was numerically higher in the 3RPT/INH arm in

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the HIV substudy. Most of the culture-confirmed TB cases in the INH arm in the HIV substudy occurred outside the US.

In the main study, there was a dose response in the 9INH arm but not in the 3RPT/INH arm. In the HIV substudy, there was no dose response in either arm. There were no TB cases in the 3RPT/INH arm in the pediatric extension study.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A dose response was observed in the 9INH arm but not the 3RPT/INH arm.

Table 36: Incidence of Culture-Confirmed TB in Adults and Culture-Confirmed or Clinical TB in Children by Percentage of Doses Received – MITT – TBTC 26 Main Study

	TB Cases	
Percentage of Doses Received	**9INH**	**3RPT/INH**
67-100%	8/3015 (0.26%)	5/3444 (0.14%)
33-67%	2/281 (0.7%)	2/203 (1.0%)
0-33%	5/449 (1.1%)	0/339 (0%)

Table 37: Incidence of Culture-Confirmed or Clinical TB at Any Age by Percentage of Doses Received – MITT Main Study

	TB Cases	
Percentage of Doses Received	**9INH**	**3RPT/INH**
67-100%	9/3015 (0.3%)	5/3444 (0.14%)
33-67%	2/281 (0.7%)	2/203 (1.0%)
0-33%	6/449 (1.3%)	2/339 (0.6%)

The CDC performed univariate analysis for percentage of doses received and the development of TB disease in each arm. Subjects in the 9INH treatment arm who completed ≤33% of their doses and 34-67% of doses were respectively 5.9 times and 3.1 times more likely to develop TB disease compared to those completing over 67% of their doses.

Table 38: Hazard Ratio of TB by Percentage of Dose – 9INH arm – MITT – TBTC 26 Main

Characteristic		Baseline	Univariate Analysis	
			HR (95% CI)	P value
% Exposure to Drug	≤33%	>67%	5.9 (1.9, 18.1)	0.002
	34-67%		3.1 (0.7, 14.5)	0.156

In the 3RPT/INH arm, there were no TB cases in the 3RPT/INH treatment arm among patients completing ≤33% of doses. Subjects who completed 34-67% of doses were 7.7 times more likely develop TB disease compared to subjects who completed over 67% of the prescribed doses.

Table 39: Hazard Ratio of TB by Percentage of Dose – 3RPT/INH arm – MITT – TBTC 26 Main Study

Characteristic		Baseline	Univariate Analysis	
			HR (95% CI)	P value
% Exposure to Drug	≤33%	>67%	0	-
	34-67%		7.7 (1.5, 39.5)	0.015

In the HIV substudy, a dose response was not noted in either treatment arm.

Reviewer's Comments
In the main study, one case of clinical TB in an adult occurred among 181 subjects who received ≤1 dose of 3RPT/INH and 3 cases of culture-confirmed TB occurred among 220 subjects who received <31 days of 9INH. The culture-confirmed TB absolute rate is 3/401 (0.75%). The rate among subjects who received no treatment (0/90 in 3RPT/INH arm plus 2/98 in 9INH arm = 3/188) was1.6%. These rates are comparable to the placebo rates reported in the previously cited IUAT trial and the Cochrane meta-analysis for HIV-negative patients.

Cumulative TB rates in HIV infected subjects who received < 2 doses of 3RPT/INH or < 31 days of 9INH was 12.5%. This rate is similar to the TB rate that is cited in the literature for untreated HIV-infected patients.

6.1.9 Additional Efficacy Issues/Analyses

In the HIV substudy, baseline CD4 was available for 7 subjects who developed culture-confirmed TB and for 359 subjects who did not develop TB. Subjects who developed TB disease had numerically lower CD4 counts.

Table 40: CD4 Count and TB Occurrence – HIV Substudy

	TB Disease N = 7	**No TB Disease N = 359**	**P Value**
CD4 median, range	344 (131-615)	510 (9-1988)	0.057

7 Review of Safety

Safety Summary

Treatment emergent adverse events were defined as those occurring during treatment and for 60 days after end of treatment. The longer duration of treatment in the 9INH arm may lead to a higher number of subjects reporting an adverse event and biases safety evaluation in favor of 3RPT/INH. Adverse events were reported for the entire regimen in the 3RPT/INH arm and not to the individual components of the combination regimen.

In the main study, a higher proportion of 9INH recipients experienced at least one treatment emergent AE or SAE, likely reflecting the longer duration of therapy. A numerically higher proportion of subjects died in the 9INH arm during the treatment emergent period or during the 33 months follow-up. A significantly higher proportion of 3RPT/INH recipients had an AE that was judged by the investigator to be treatment related or had the drug discontinued due to treatment related adverse event.

Because the legacy CDC datasets did not conform to CDISC standards, the sponsor contracted an organization that mapped the original data to a new AE dataset. Both the legacy and converted datasets were submitted. Because of differences in coding, there were numerical differences in some categories. The most significant difference pertained to hypersensitivity reactions. The legacy dataset indicated patients as having rifamycin hypersensitivity reaction using a pre-specified definition for these events which were also flagged as flu-like illness. These events were all coded under the System Organ Class, Immune System. The new dataset coded each symptom constituting the hypersensitivity reaction individually under the corresponding SOC, resulting in major discrepancies in the number of events noted in eye, gastrointestinal, general, immune, musculoskeletal, respiratory and skin organ systems.
The main toxicity associated with INH was hepatic, occurring in approximately 3% of the population. Hepatic toxicity occurred less frequently in the 3RPT/INH arm, occurring in approximately 0.6%. In both treatment arms, hepatic toxicity was more frequent in subjects who were HIV, HCV or HBV infected and in subjects with history of alcohol use. Most of the hepatic toxicity cases were attributed to INH in the 9INH and all the hepatic toxicity events were attributed to 3RPT/INH in the combination arm. Hepatic toxicity was the most common cause of treatment discontinuation in the 9INH arm.

In comparison, hypersensitivity reaction was the main toxicity associated with 3RPT/INH, occurring in 4% of subjects, and was the most common cause of treatment discontinuation in the 3RPT/INH arm. Hypersensitivity reactions in the 3RPT/INH arm were more common in women compared to men.

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Most SAEs were judged unrelated to study treatment. In the 9INH arm, treatment related SAEs were hepatic in three of seven subjects and hypersensitivity in 2 subjects. In the 3RPT/INH arm, treatment related SAEs in ten of fourteen subjects were hypersensitivity reactions.

Seventy-one deaths occurred in the study at 33 months follow-up, 40 in the INH arm and 31 in the 3RPT/INH arm. None of the deaths was judged as drug related.

Ten subjects in each arm had lab changes that satisfied Hy's law during treatment. There were no cases of hepatic failure and no cases that required transplant. None of the deaths was due to drug related hepatic injury. There were no significant changes in hematologic parameters or renal function.

In the main study, there was significant variation in the frequency of AEs reported between study sites. However, the pattern of toxicities noted within each site was similar to the overall pattern in the study. More AEs were reported in the US/Canada compared to Brazil/Spain.

No cases of hepatic toxicity were noted in the pediatric substudy in either treatment arm, and the frequency of hypersensitivity was lower compared to the main study. No hypersensitivity cases occurred in the subset of children 2-11 years of age. In the HIV substudy, the frequency of hepatic toxicity was higher in both treatment arms compared to the main study (approximately double), but the frequency of rifamycin hypersensitivity was considerably lower, with only one case reported.

A total of one hundred and sixteen (116) pregnancies occurred in the treatment emergent period, 71 in the 9INH arm and 45 in the 3RPT/INH arm. Spontaneous abortion occurred in nine (12.7%) and seven (15.6%) pregnancies in the 9INH and 3RPT/INH arms respectively. One of the spontaneous abortions in the 3RPT/INH arm was a non-viable female fetus with a large cystic mass on the neck and Downs syndrome. One of the elective abortions in the 3RPT/INH arm had Turner's syndrome.

Post-marketing experience with rifapentine does not add new safety information with the exception that four of fourteen (4/14, 29%) of pregnancies reported to the sponsor ended in spontaneous abortion. Review of the literature does not add new safety information.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Data from main TBTC Study 26 and TBTC Study 26 pediatric and HIV substudies will be presented in detail. A description of the safety data from the two PK studies, INT 12099 and

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12991 in healthy subjects will be summarized. Studies Martinson et al. and Schecter et al. have already been summarized in Section 5 of this review.

7.1.2 Categorization of Adverse Events

Treatment-emergent AEs were defined as the AEs that occurred from the start of treatment to 60 days after the last dose of the study drug, regardless of the relationship to treatment. Relationship to treatment was determined by the investigator, and considered in relationship to the entire regimen for patients in the 3RPT/INH arm rather than the individual components of the combination. AE severity was reported using NCI CTC v.2.0 grading.

Table 41: Adverse Event Grading – NCI CTC v.2.0

	Definition
Grade 1	Transient or mild discomfort, no limitation in activity; no medical intervention/therapy required
Grade 2	Mild to moderate limitation in activity, some assistance usually required; no or minimal medical intervention/therapy required
Grade 3	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible
Grade 4	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization possible
Grade 5	Death

Reviewer's Comments
The definition of a treatment emergent adverse event as occurring during treatment or during the 60 days after last dose of study treatment is acceptable, given the half-life of the drugs.

The applicant submitted two adverse events analysis datasets, one of which was labeled as CDC legacy. There were differences between the two datasets.

- Differences in assigning AE terms to System Organ Class:
  - Bronchitis and sinusitis were coded under Infections and Infestations SOC in the legacy dataset and under Respiratory SOC in the applicant's dataset, with different numerical results.
  - Dizziness was coded under Nervous System SOC in the legacy dataset and under Vascular System in the applicant's dataset.
  - The legacy dataset used the AE term hepatitis under the pre-specified event category of hepatotoxicity. The converted datasets used the AE term hepatotoxicity to indicate hepatic adverse reaction.
  - The converted dataset coded the verbatim terms rash, dizziness, headache, red eyes, fever, arthralgia and myalgia to their respective MedDRA PT and MedDRA SOC individually. The legacy dataset lumped the above events under the term

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"drug associated reaction" and the code "hypersensitivity" using a pre-specified definition for rifamycin hypersensitivity reaction (see AEs of special interest). The rifamycin hypersensitivity reactions were also flagged as "flu-like Illness" in the legacy data and "toxicity to various agents" in the converted data. For INH, the legacy data also lumped some terms (rash, chills, aches) to the code "hypersensitivity" and coded rash only as "skin reaction", whereas the converted dataset used the AE term "drug related toxicity" and the AE code "toxicity to various agents" to indicate hypersensitivity reactions, skin reactions and some cases of hepatitis. This resulted in major discrepancies in the frequency of adverse events coded under Eye, Gastrointestinal, General, Musculoskeletal, Immune, and Skin Disorders, and under Injury/Poisoning/Procedural Complications System Organ Classes.

- The legacy dataset excluded some patients who died from the total number of subjects who had an AE.
- One of the deaths in the INH arm had TB and the outcome was classified as TB, not as death in legacy dataset.
- Relatedness to treatment was categorized as definite, possible, probable, unlikely, unrelated or unknown in the legacy dataset. The AEs classified as definite, probable or possible were considered drug related. Relatedness was re-categorized as related or not related in the converted data, resulting in differences in the number of patients who had a treatment related AE.
- The legacy tabulation AE dataset and the converted analysis AE datasets both characterized action taken for an AE as "drug interrupted", "drug withdrawn", "dose not changed" or "unknown". 98 subjects flagged as having permanently discontinued treatment due to treatment related AE in both legacy and analysis AE datasets were not included in the drug withdrawn category, but were included in the drug interrupted or no change categories. The number of subjects who discontinued treatment due to an adverse reaction may not be accurately reported.

Similar to the main study, two AE analysis datasets were submitted for each of the pediatric and HIV substudies, one legacy and one converted to conform to CDISC standards, with the similar coding differences.

Unless specified as legacy data, the source of safety data presented was the converted datasets.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data will not be pooled across studies because the populations enrolled in the main study and in the pediatric and HIV substudies overlapped, and the two PK studies enrolled less than 1% of the

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population enrolled in the main study and subjects received either a single dose or a shorter duration of exposure.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations

The safety population in the main Study included 3759 in the 9INH arm and 4040 in the 3RPT/INH arm.

Table 42: Extent of Exposure – TBTC 26 – Main Study

	9INH N = 3759	3RPT/INH N = 4040
Doses Taken		
Mean (SD)	219.8 (78.0)	10.8 (2.9)
Median (Range)	256 (1-298)	12 (1-17)
Weeks on Therapy		
Mean (SD)	37.0 (13.4)	11.2 (3.4)
Median (Range)	40 (1-90)	12 (1-34)

Table 43: Summary of Exposure – Pediatric Substudy

	9INH			3RPT/INH		
	2-11 yrs N = 230	12-17 yrs N = 263	Total N = 493	2-11 yrs N = 292	12-17 yrs N = 247	Total N = 539
Doses Taken						
Mean	202.9	234.4	219.7	10.6	11.3	11.0
(SD)	(90.2)	(58.4)	(76.5)	(2.92)	(2.2)	(2.6)
Median	250.5	254	253	12	12	12
(Range)	(1-291)	(25-292)	(1-292)	(1-13)	(1-13)	(1-13)
Weeks on Rx						
Mean	33.5	39.9	36.6	11.2	11.5	11.4
(SD)	(14.6)	(10.8)	(13.1)	(3.3)	(2.6)	(3.0)
Median	40	40	40	12	12	12
(Range)	(2-63)	(5-76)	(2-76)	(1-20)	(1-23)	(1-23)

Reviewer's Comments

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The mean number of INH doses and weeks on therapy were higher among adolescents than among younger children, but the median numbers were similar. There were no significant differences in the 3RPT/INH arm.

Table 44: Summary of Exposure – HIV Substudy

	9INH N = 186	3RPT/INH N = 207
Doses Taken		
Mean (SD)	230.5 (72.9)	11.4 (2)
Median (Range)	220 (7-283)	11 (1-13)
Weeks on Rx		
Mean (SD)	36.7 (11.8)	11.6 (2.3)
Median (Range)	39.4 (1-66)	11.3 (1-18)

Concomitant medications were not reported by category, but by individual drug name. The most frequently reported concomitant medications used by ≥5% in each arm were multivitamins and NSAIDs (mainly ibuprofen). Other medications included a variety of anti-hypertensive agents (beta blocker, calcium channel blockers, ACE inhibitors and ARBs) and were balanced between the treatment arms. 142 subjects were on methadone, 72 in the INH arm and 70 in the 3RPT/INH arm.

7.2.2 Explorations for Dose Response

Adult subjects received 900 mg RPT and 900 mg INH weekly. Children received weight based dosing of RPT. Although RPT exposure in children was higher than in adults, there were no cases of hepatotoxicity in children and the frequency of hypersensitivity reactions was lower compared to that in adults.

7.2.3 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Rifamycins are associated with hepatic toxicity. Intermittent administration and high doses have been associated with a hypersensitivity reaction that is thought to be immune mediated and that manifests mainly as a flu-like illness.

In TBTC Study 26, hepatotoxicity was defined as AST≥3xULN in the presence of specific signs and symptoms of hepatitis, or AST>5xULN regardless of signs or symptoms. Rifamycin hypersensitivity/flu-like syndrome was defined as follows: either a) one of the following: hypotension, urticaria, angioedema, acute bronchospasm, or conjunctivitis occurring in relation

to study drug or b) at least 4 of the following symptoms occurring in relation to the study drug, with ≥1 symptom being Grade 2 or higher: weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, SOB, flushing or chills.

7.3 Major Safety Results

Table 45: Summary of Treatment Emergent AEs – TBTC Study 26 Main – Legacy Dataset

	9INH N = 3759	3RPT/INH N = 4040	P value
Subjects with at least one AE	661 (17.6%)	595 (14.7%)	0.0006
Subjects with treatment-related AE	206 (5.5%)	332 (8.2%)	<0.0002
D/C treatment due to AE	223 (5.9%)	272 (6.7%)	0.147
D/C treatment due to treatment related AE	142 (3.8%)	196 (4.9%)	0.02
Subjects with any SAE	109 (2.9%)	64 (1.6%)	<0.0002
Subjects with any treatment related SAE	6 (0.2%)	13 (0.3%)	0.147
Died within 60 days of last drug dose	7 (0.2%)	4 (0.1%)	0.482
Died within 33 months from enrollment	39 (1.0%)	31 (0.8%)	0.206

Table 46: Summary of Treatment Emergent AE – TBTC Study 26 – Applicant Dataset

	9INH N = 3759	3RPT/INH N = 4040	P value
Subjects with at least one TEAE	667 (17.7%)	597 (14.8%)	0.0004
Subjects with treatment related TEAE	225 (6.0%)	352 (8.7%)	<0.0002
D/C treatment due to TEAE	223 (5.9%)	273 (6.7%)	0.136
D/C treatment due to treatment related TEAE	142 (3.8%)	196 (4.9%)	0.02
Subjects with any TE SAE	112 (3.0%)	65 (1.6%)	<0.0002
Subjects with any treatment related SAE	7 (0.2%)	14 (0.3%)	0.172
Died within 60 days of last drug dose	7 (0.2%)	4 (0.1%)	0.482
Died within 33 months from enrollment	40 (1.1%)	31 (0.8%)	0.206
All deaths at close of study	45 (1.2%)	34 (0.8%)	0.117

Reviewer's Comments
The reported AEs in the 3RPT/INH arm pertain to the entire regimen and not to the individual drugs. Because treatment emergent AEs were captured during and within 60 days of treatment, the longer duration of 9INH therapy biases the safety evaluation in favor of 3RPT/INH. This is acceptable because it is the safety of the entire regimen (dosing and duration) that needs to be evaluated.

A higher proportion of subjects experienced a treatment emergent AE or SAE or died in the 9INH arm. This likely reflects the longer duration of treatment in the 9INH arm compared to the

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3RPT/INH arm. Despite the shorter duration of therapy, a higher proportion of subjects in the 3RPT/INH experienced a treatment related AE and discontinued therapy due to treatment related AE.

Table 47: Summary of AE – Pediatric Substudy

	9INH			3RPT/INH		
	2-11 yrs N = 230	**2-17 yrs N = 263**	**Total N = 493**	**2-11 yrs N = 292**	**2-17 yrs N = 247**	**Total N = 539**
Subjects with any TEAE	41 (17.8%)	22 (8.4%)	63 (12.8%)	30 (10.3%)	22 (8.9%)	52 (9.6%)
D/C due to AE	3 (1.3%)	4 (1.8%)	7 (1.4%)	4 (1.4%)	5 (2.0%)	9 (1.7%)
Treatment related AE*	5 (2.2%)	1 (0.4%)	6 (1.2%)	7 (2.4%)	8 (3.2%)	15 (2.8%)
D/C due to Treatment related AE	2 (0.9%)	1 (0.4%)	3 (0.6%)	3 (1.0%)	5 (2.0%)	8 (1.5%)
SAE	3 (1.3%)	4 (1.5%)	7 (1.4%)	0	0	0
Treatment related SAE	0	0	0	0	0	0
Died	0	2 (0.8%)	2 (0.4%)	0	0	0

Reviewer's Comments
Similar to the main study, a higher proportion of 9INH subjects experienced at least one treatment emergent AE, likely reflecting the longer duration of therapy. Also similar to the main study, a higher proportion of 3RPT/INH subjects had an AE that was assessed as treatment related and discontinued therapy due to treatment related AE. There were no SAEs or deaths reported in the 3RPT/INH arm.

The proportion of subjects experiencing at least one AE was higher in the 2-11 age group compared to the 12-17 age group.

Table 48: Summary of AEs – HIV Substudy

	9INH N = 186	**3RPT/INH N = 207**
Subjects with at least one AE	75 (40.3%)	45 (21.7%)
Treatment related AE	21 (11.3%)	15 (7.2%)
Discontinued due to treatment related AE	8 (4.3%)	7 (3.4%)
SAE	21 (11.3%)	8 (3.9%)
Treatment related SAE	2 (1.1%)	5 (2.4%)
Died during treatment or within 60 days of last dose	1 (0.5%)	0

Died during 33 months FU	5 (2.7%)	6 (2.9%)

Reviewer's Comments
The proportion of subjects experiencing an AE was higher in both treatment arms compared to the main study.

Similar to the main study and pediatric substudy, a higher proportion of 9INH recipients experienced an AE or SAE compared to 3RPT/INH recipients. Unlike the main study and the pediatric substudy, the proportion of 9INH discontinuing treatment due to treatment related AEs was higher compared to 3RPT/INH recipients in the HIV substudy.

Safety in the PK Studies INT12099 and 12291

Seventeen (17) subjects were enrolled in Study 12099 and 15 completed the study. There were no SAEs. One subject discontinued the study due to an AE (elevated BP and heart rate) 4 days after INH fasted administration. The most frequent AEs among subjects who received rifapentine were nasal congestion, dysuria, nausea, vomiting, and urinary discoloration (chromaturia). Only chromaturia was judged drug related. No subject developed elevated ALT, AST, bilirubin or alkaline phosphatase, and no subject developed changes in Cr, electrolytes or glucose.

Twelve (12) HIV infected subjects were enrolled in Study 12291, 10 males and 2 females, 5 white and 7 black. All had a CD4 count of at least 350 and undetectable viral load. Eleven (11) had been on Atripla for at least 3 months prior to enrollment and one had been on Atripla for 4 weeks prior to enrollment. There were no SAEs and no AEs that resulted in drug discontinuation. 3 (25%) subjects had an AE while receiving Atripla alone, and 11 (91.7%) had an AE while receiving both drugs. AEs that occurred during the Atripla/rifapentine period included nasopharyngitis, decreased appetite, headache, somnolence, dizziness, oropharyngeal pain, nausea, dyspepsia and arthralgia. The most common AE was chromaturia, occurring in 10/12 (83.3%) subjects during the Atripla/rifapentine period and in no subject during the Atripla administration period.
No subject developed an elevation of ALT or AST or bilirubin or alkaline phosphatase. No subject developed an elevation in Cr or an electrolyte abnormality or change in glucose metabolism. One subject had borderline baseline thrombocytopenia and no further hematologic changes were noted. There were no changes in vital signs. One subject had borderline QT prolongation at baseline. No subject had QTc interval change compared to baseline. There were also no changes in viral load or CD4 parameters.

Reviewer's Comments
Rifamycins predictably result in discoloration of body secretions, which was noted in these PK studies, but was not reported in main Study 26 or the pediatric or HIV substudy. The reasons for

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lack of reporting is unclear, but may be related to the familiarity of TB investigators with these reactions.

7.3.1 Deaths

Eleven subjects died within 60 days of the last dose of study treatment in the main study. At 33 months after enrollment, 71 subjects died (70 according to legacy data – the outcome of one subject who died was coded as TB, not also as death). By the conclusion of the study in November 2010, there were 80 deaths in the ITT population, of which 79 were in the safety population.

Table 49: Deaths – TBTC Study 26 Main

Deaths	9INH N = 3759	3RPT/INH N= 4040
Within 60 days of last drug dose	7 (0.2%)	4 (0.1%)
At 33 months after enrollment	40 (1.1%)	31 (0.8%)
At conclusion of study November 2010	45 (1.2%)	34 (0.8%)

Table 50: Causes of Death – ICD9 Categories – TBTC Study 26 Main

At 33 months post enrollment	9INH N = 40	3RPT/INH N = 31
AIDS	1	1
Cerebrovascular disease	1	4
Chronic liver disease	2	4
Chronic lower respiratory di	1	0
Chronic pancreatitis	1	0
Diabetes mellitus	1	0
Diseases of the heart	4	8
Hypertension	2	1
Intentional injuries	6	1
Malignant neoplasms	15	8
Septicemia	1	1
Unintentional injuries	3	3
Unknown	2	0
Within 60 days of last study dose	**9INH N = 7**	**3RPT/INH N = 4**
Cerebrovascular disease	0	1
Chronic liver disease	1	0
Chronic lower respiratory disease	1	0
Diseases of the heart	2	2

Malignant neoplasms	1	1
Unintentional injuries	2	0

Reviewer's Comments
Narratives for 70 subjects who died in the main study during the 33 months study duration were reviewed. I agree that none of the deaths is attributed to the study drug. One additional subject was not counted in the legacy dataset because he had TB as an outcome (subject 2868). This subject was a 59 year old HIV-negative male who took 253 INH doses over 447 days and missed his first follow up appointment as well as his month 4 and 5 appointments. His last INH dose was on July 12, 2005. In August 2005, he presented with cough, fevers and night sweats. CXR showed cavities and right pleural effusion. Sputum culture grew drug-sensitive TB, and he was started on INH, rifampin, ethambutol and PZA on August 19, 2005. His symptoms improved but he was not compliant with therapy and was difficult to locate. He was confined to the hospital for TB treatment and died on (b) (4) *(Study Day* (b) (4) *). An autopsy was performed and death was attributed to respiratory failure due to COPD, with TB and pulmonary embolism as contributing factors. Death certificate listed COPD as the cause of death.*

The characteristics of the subjects who died were similar between the treatment arms for age, sex, race and country of enrollment. The proportion of HIV infected subjects who died in the 9INH arm was higher compared to the overall population or to other subgroups, but the numbers are small. Causes of death in the two children who died in the 9INH arm were gunshot wounds and sudden death due to arrhythmia.

Table 51: Characteristics of Subjects who Died by 33 Months after Enrollment – Study 26 Main

	9INH N = 3759	**3RPT/INH N = 4040**
Deaths	40 (1.1%)	31 (0.8%)
Median age	54 (16-88)	55 (39-77)
Age Group		
≥18	37/3417 (1.1%)	31/3692 (0.8%)
12-17	2/342 (0.6%)	0/348
Male	30/2013 (1.5%)	22/2242 (1.0%)
Female	10/1746 (0.6%)	9/1798 (0.5%)
White	16/2184 (0.7%)	18/2343 (0.8%)
Black	19/935 (2.0%)	10/981 (1.0%)
Asian	2/489 (0.4%)	3/493 (0.6%)
American Indian	1/33 (0.3%)	0/83
Other	2/118 (1.7%)	0/140
Brazil	3/415 (0.7%)	5/470 (1.1%)
USA/Canada	37/3344 (1.1%)	26/3570 (0.7%)

HIV positive	3/95 (3.2%)	1/105 (1.0%)
HIV negative	20/1760 (1.1%)	16/1775 (0.9%)
HIV unknown	17/1904 (0.9%)	14/2160 (0.6%)

Reviewer's Comments

Two deaths occurred in the pediatric substudy, both in children enrolled in the main study. No deaths occurred in the extension phase. Both deaths were in the 9INH arm, one occurred during the treatment period and one occurred during the follow up period. The first death was a 16 year old HIV negative female Asian Pacific Islander enrolled in Canada who received 195 doses of INH. She was found dead in her bedroom on Study Day 201. An autopsy was performed and cause of death reported as "malignant arrhythmia". She was on iron and pyridoxine but no other medications at time of death. The death was judged not drug related. There is not enough information regarding the autopsy findings for me to judge relatedness. The second death was a 16 year old HIV negative Hispanic male who completed 218 INH doses. On Study Day 901, approximately 94 weeks after last dose of study medication, he died as a result of multiple gunshot wounds. I agree that this death was not drug related.

In the HIV substudy, three of the five subjects who died in the 9INH arm were enrolled in the main study. One subject died during the treatment period or within 60 days of the last dose. This subject was a 36 year old man with history of hepatitis B infection and liver cirrhosis. He received 130 doses of INH and died on study day 131. An autopsy was performed and the cause of death was classified as chronic liver disease. The death was judged not to be drug related. Four subjects died during the 33 months follow up period. Causes of death included hypertension, AIDS dementia, septic shock with pneumonia and metastatic cervical cancer. One of the six subjects who died in the 3RPT/INH arm was enrolled in the main study. All six subjects died during the 33 months follow up period. Causes of death included AIDS, complicated sickle cell disease, septic shock with pneumonia, AIDS with non-Hodgkin's lymphoma, intentional injuries and unknown.

Narratives were reviewed. I agree that none of the deaths are related to study regimen. Review of the labs of the HIV infected patient in the INH arm who died during therapy and whose death was indicated as chronic liver disease does not reveal evidence of superimposed hepatic injury.

7.3.2 Nonfatal Serious Adverse Events

Table 52: SAE Occurring in ≥2 subjects – TBTC 26 Main – Legacy Data

	9INH N = 3759	3RPT/INH N = 4040
Any SAE	**109 (2.9%)**	**64 (1.6%)**
Blood and lymph Disorders	3 (0.07%)	1 (0.02%)
Anemia	3 (0.07%)	1 (0.03%)
Gatrointestinal Disorders	15 (0.4%)	6 (0.15%)
Abdominal pain	3 (0.07%)	0
Pancreatitis	2 (0.05%)	2 (0.05%)
Vomiting	3 (0.07%)	0
Hepatobiliary Disorders	12 (0.3%)	7 (0.15%)
Hepatitis	11 (0.3%)	4 (0.1%)
Injury/Poisoning	**16 (0.4%)**	**4** (0.1%)
Ankle fracture	2 (0.05%	0
Medication error	2 (0.05%)	1 (0.03%)
Immune System	**2 (0.05%)**	**10 (0.25%)**
Hypersensitivity	2 (0.05%)	10 (0.25%)
Nervous system	**9 (0.2%)**	**5** (0.1%)
Syncope	3 (0.07%)	0
Pregnancy/Pueperium	**2 (0.05%)**	**5** (0.1%)
Pregnancy	2 (0.05%)	5 (0.1%)
Psychiatric	**13 (0.4%)**	**4** (0.1%)
Depression	3 (0.07%)	1 (0.02%)
Depression suicidal	2 (0.05%)	0
Suicidal ideation	2 (0.05%)	0
Suicide attempt	2 (0.05%)	0
Vascular	**7 (0.15%)**	**2** (0.05%)
Hypertension	3 (0.07%)	2 (0.05%)

Table 53: SAE Occurring in ≥2 subjects – TBTC 26 Main – Applicant Data

	9INH N = 3759	3RPT/INH N = 4040
Any SAE	**112 (3.0%)**	**65 (1.6%)**
Blood and lymph Disorders	3 (0.07%)	1 (0.02%)
Anemia	3 (0.07%)	1 (0.03%)
Gatrointestinal Disorders	16 (0.4%)	9 (0.3%)
Abdominal pain	3 (0.07%)	0
Pancreatitis	2 (0.05%)	2 (0.05%)
Vomiting	5 (0.1%)	4 (0.1%)
General Disorders	4 (0.1%)	4 (0.1%)
Pyrexia	0	2 (0.05%)
Hepatobiliary Disorders	4 (0.1%)	4 (0.1%)
Hepatotoxicity	3 (0.07%)	1 (0.02%)
Immune Disorders	1 (0.02%)	2 (0.05%)
hypersensitivity	1 (0.02%)	2 (0.05%)
Injury/Poisoning	11 (0.3%)	2 (0.05%)
Ankle fracture	3 (0.07%)	0
Pregnancy/Puerperium	3 (0.07%)	4 (0.1%)
Pregnancy	2 (0.05%)	4 (0.1%)
Psychiatric Disorders	14 (0.4%)	4 (0.1%)
Depression	4 (0.1%)	1 (0.02%)
Depression suicidal	2 (0.05%)	0
Suicidal ideation	4 (0.1%)	0
Suicidal attempt	2 (0.05%)	0
Respiratory Disorders	23 (0.6%)	8 (0.2%)
Chest pain	7 (0.2%)	3 (0.07%)
Cough	2 (0.05%)	0
Dyspnea	3 (0.07%)	1 (0.02%)
Pneumonia	4 (0.1%)	2 (0.05%)
Skin/SC Disorders	3 (0.07%)	5 (0.1%)
Cellulitis	2 (0.05%)	2 (0.05%)
Vascular Disorders	13 (0.3%)	15 (0.4%)
Dizziness	1 (0.02%)	0
Hypertension	5 (0.1%)	1 (0.02%)
Syncope	2 (0.05%)	2 (0.05%)

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Cerebrovascular accident	0	2 (0.05%)
GI hemorrhage	0	2 (0.05%)

Seven subjects in the 9INH arm had nine SAEs assessed as treatment related: depression (suicidal), dizziness, headache, hepatotoxicity (3 subjects), hypersensitivity and vomiting (2 subjects).

Fourteen subjects in the 3RPT/INH arm had 26 SAEs assessed as treatment-related: abdominal pain, chills, chocking, diarrhea, drug hypersensitivity, gout, hematemesis, hepatotoxicity, hypotension, migraine, ocular hyperemia, pain, palpitations, pancreatitis (2 subjects), pneumonia, pyrexia (2 subjects), rash, syncope (2 subjects), thalamic infarct, vomiting (2 subjects). Ten were hypersensitivity reactions.

Reviewer's Comments
Differences in coding mainly pertaining to hypersensitivity reactions resulted in differences detailed in the above tables.

A higher proportion of subjects in the 9INH arm experienced a serious AE, likely reflecting the longer duration of treatment. The main SAEs in the 3RPT/INH arm were hypersensitivity reactions and hepatitis. The main SAE in the 9INH arm was hepatitis, which was more frequent than in the 3RPT/INH arm. Depression was reported in a higher proportion of 9INH subjects. Although depression has been reported in association with INH, the drug historically ushered the era of antidepressant therapies when it was observed to be associated with euphoria in TB patients.
The narratives for SAEs were reviewed. I agree with causality attribution regarding hepatotoxicity and hypersensitivity reaction symptoms. Symptoms of hypersensitivity reaction in subjects exposed to rifapentine included red eyes, palpitations, diarrhea, vomiting, headache, hypotension, rigors, body aches, fatigue, stomach pain, fever, chills, flushing, rash, myalgia, arthralgia, cough, difficulty breathing, syncope, worsening anemia, thrombocytopenia and neutropenia.

In the pediatric substudy, seven subjects had a serious AE, all in the 9INH arm: ankle fracture, bronchial hyperreactivity, death, depression, Kawasaki disease, status asthmaticus and vomiting. None of the SAEs were judged as treatment related. Narratives for SAEs were reviewed. I agree that none are likely to be drug related. There were no SAEs in the 3RPT/INH arm.

In the HIV substudy, twenty one subjects in the 9INH arm experienced at least one SAE: anemia (2), CHF (1), abdominal pain (2), hepatotoxicity (2), wound infection (1), cellulitis (1), ankle fracture (1), drug overdose (1), suicidal ideation (1), suicide attempt (2), hernia repair (1), appendectomy (1), hypertensive crisis (1), myocardial infarction (1), deep vein thrombosis (1), rectal hemorrhage (1) and syncope (1). All were judged as unrelated to drug except for the two subjects with hepatotoxicity.

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Eight subjects in the 3RPT/INH arm experienced a SAE: overdose (1), ankle operation (1), depression (1), myositis (1), pancreatitis (1), pyrexia (1), thalamic infarct (1) and syncope (1). Five were judged by the investigator to be drug related: pancreatitis, pyrexia, thalamic infarct, myositis and depression. Three of the five subjects were enrolled in the main study. I agree that pyrexia was likely drug related.

7.3.3 Treatment Discontinuation Due to Adverse Reaction

The legacy tabulation and the legacy and converted analysis datasets both indicate that a total of 407 subjects had the "drug withdrawn" due to an AE. Both datasets also flagged a total of 338 subjects as having the drug discontinued due to a treatment related AE, but only 240 of these 338 subjects are indicated as having the "drug withdrawn" due to an AE in either the legacy or converted datasets. The other 98 subjects who permanently discontinued the drug due to an adverse event were categorizes as "drug interrupted", "no action" or "unknown". The tables below were generated by including all subjects flagged as having the drug withdrawn and all subjects flagged as having the drug discontinued due to treatment related AE.

Table 54: Treatment Discontinuation due to AE Occurring in ≥5 subjects – TBTC 26 Main – Legacy

	9INH N = 3759	3RPT/INH N = 4040
D/C due to AE	**223 (5.9%)**	**272 (6.7%)**
Gastrointestinal Disorders	**7 (0.2%)**	**22 (0.6%)**
Nausea	9 (0.2%)	9 (0.2%)
General/Administration Site	**14 (0.4%)**	**27 (0.7%)**
Fatigue	8 (0.2%)	6 (0.15%)
Hepatobiliary System	**80 (2.1%)**	**13 (0.4%)**
Hepatitis	79 (2.1%)	12 (0.3%)
Immune System	**17 (0.5%)**	**131 (3.2%)**
Hypersensitivity	17 (0.5%)	131 (3.2%)
Nervous System	**16 (0.4%)**	**13 (0.4%)**
Headache	8 (0.2%)	10 (0.3%)
Pregnancy	**46 (1.2%)**	**24 (0.6%)**
Pregnancy	45 (1.2%)	24 (0.6%)

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Table 55: Treatment Discontinuation Due to AE Occurring in ≥5 Subjects – TBTC 26 Main – Applicant Data

MedDRA v. 14.0 System Organ Class Preferred Term	**9INH N = 3759**	**3RPT/INH N = 4040**
D/C treatment due to AE	**223 (5.9%)**	**272 (6.7%)**
Eye Disorders	**0**	**9 (0.2%)**
Ocular hyperemia	0	9 (0.2%)
Gastrointestinal Disorders	**11 (0.3%)**	**63 (1.6%)**
Diarrhea	2 (0.05%)	6 (0.15%)
Nausea	11 (0.25%)	20 (0.4%)
Vomiting	4 (0.1%)	28 (0.7%)
General Disorders	**25 (0.6%)**	**107 (2.6%)**
Asthenia	0	10 (0.25%)
Chills	2 (0.05%)	17 (0.4%)
Fatigue	15 (0.4%)	24 (0.6%)
Flu-like illness	0	25 (0.6%)
Pyrexia	3 (0.1%)	30 (0.7%)
Hepatobiliary Disorders	**80 (2.1%)**	**13 (0.3%)**
Hepatotoxicity	79 (2.1%)	12 (0.3%)
Immune System Disorders	**2 (0.05%)**	**19 (0.5%)**
Hypersensitivity	2 (0.05%)	15 (0.4%)
Drug Hypersensitivity	0	4 (0.1%)
Injury/Poisoning	**48 (1.2%)**	**97 (2.4%)**
Toxicity to various agents	46 (1.2%)	97 (2.4%)
Musculoskeletal Disorders	**12 (0.3%)**	**28 (%)**
Arthralgia	4 (0.1%)	8 (0.2%)
Myalgia	2 (0.05%)	17 (0.4%)
Nervous System Disorders	**19 (0.5%)**	**37 (0.9%)**
Headache	14 (0.4%)	39 (1.0%)
Pregnancy/Puerperium/Perinatal	**46 (1.2%)**	**24 (0.6%)**
Pregnancy	45 (1.2%)	24 (0.6%)
Respiratory Disorders	**7 (0.2%)**	**12 (0.3%)**
Dyspnea	4 (0.1%)	10 (0.25%)
Skin and SC Disorders	**31 (0.8%)**	**52 (1.2%)**
Rash (any)	22 (0.5%)	31 (0.7%)
Urticaria	4 (0.1%)	11 (0.3%)
Vascular Disorders	**11 (0.25%)**	**30 (0.7%)**
Dizziness	8 (0.1%)	20 (0.5%)

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Flushing	0	4 (0.1%)

Table 56: Treatment Discontinuation Due to Treatment Related AE Occurring in ≥5 Subjects – TBTC 26 Main - Legacy

	9INH N = 3759	3RPT/INH N = 4040
D/C due to treatment related AE	**142 (3.8%)**	**196 (4.9%)**
Hepatobiliary Disorders		
Hepatitis	76 (2.0%)	12 (0.3%)
Immune Disorders		
Hypersensitivity	15 (0.4%)	120 (3.0%)
Skin Disorders		
Skin Reactions	13 (0.3%)	18 (0.45%)

Reviewer's Comments
In the main study, adverse reactions leading to drug discontinuation were mainly related to pregnancy, and to hepatitis/hepatotoxicity in the 9INH arm and to symptoms of hypersensitivity/flu-like reaction in the 3RPT/INH arm. Of note, pregnancy prevention was not required in the protocol.

Treatment related AEs leading to drug discontinuation were mainly hepatotoxicity in the 9INH arm and hypersensitivity in the 3RPT/INH arm. A significantly higher proportion of subjects discontinued treatment due to treatment related AEs in the 3RPT/INH arm despite the shorter duration of treatment. The severity grade of the AEs that led to treatment discontinuation was similar in the two treatment arms (see secondary endpoints, efficacy section). A possible explanation could be the fact that hypersensitivity is a clinical syndrome with symptoms that manifest 2-4 hours after drug ingestion, whereas hepatotoxicity may be asymptomatic and detected on laboratory examination done monthly. A physician may be more likely to withdraw the drug for a clinical symptomatic reaction.

In the pediatric substudy, seven subjects in the 9INH arm discontinued treatment due to an AE: asthenia (1), pregnancy (3), rash (2) and Kawasaki disease (1). The AEs that led to discontinuation were judged treatment related in 3 subjects: asthenia (1), rash (2).
Nine subjects in the 3RPT/INH arm discontinued treatment due to an AE: flu-like illness (2), fatigue (1), drug intolerance (1), drug toxicity (2), decreased appetite (1), rash (1) and urticaria (1). The AEs that led to drug discontinuation were judged as treatment related in 8 subjects: flu-like illness (2), rash (1), urticaria (1), fatigue (1), vomiting (1), drug intolerance (1) and lip blisters (1). Four of the eight subjects in the 3RPT/INH arm were coded as hypersensitivity reaction in the legacy dataset.

In the HIV substudy, eight subjects in the 9INH arm discontinued treatment due to hepatotoxicity. All 8 were judged treatment related. Seven subjects in the 3RPT/INH arm discontinued treatment due to a treatment related AE: hepatitis (2), pyrexia (1), hypersensitivity reaction (1), thalamic infarct (1), myositis (1) and confusional state with hallucinations and restlessness (1).

7.3.4 Significant Adverse Events

Table 57: Treatment Emergent AEs Occurring in ≥0.5% of subjects – TBTC Study 26 Main – Legacy Data

MedDRA v.14.0 System Organ Class AE Code	9INH N = 3759	3RPT/INH N = 4040
Subjects with at least one TEAE	661 (17.6%)	595 (14.7%)
Infections and Infestations	162 (4.3%)	76 (1.9%)
Bronchitis	22 (0.6%)	6 (0.2%)
Sinusitis	18 (0.5%)	4 (0.1%)
Immune System Disorders	20 (0.5%)	163 (4.0%)
Hypersensitivity	18 (0.5%)	161 (4.0%)
Hepatobiliary System Disorders	**116 (3.1%)**	**28 (0.7%)**
Hepatitis	113 (3.0%)	24 (0.6%)
Injury, Poisoning, and Procedural Complications	**89 (2.4%)**	**50 (1.2%)**
Medication error	37 (1.0%)	27 (0.7%)
Pregnancy, Puerperium and Perinatal Conditions	**72 (1.9%)**	**45 (1.1%)**
Pregnancy	71 (1.9%)	45 (1.1%)
Nervous System Disorders	**49 (1.3%)**	**47 (1.2%)**
Headache	17 (0.5%)	26 (0.6%)
Skin and Subcutaneous Disorders	**40 (1.1%)**	**43 (1.1%)**
Skin reaction	21 (0.6%)	31 (0.8%)

Table 58: Treatment Emergent AEs occurring in ≥0.5% of Subjects and Selected AEs occurring at <0.5% –Applicant Dataset

MedDRA v. 14.0 System Organ Class Preferred Term	9INH N = 3759	3RPT/INH N = 4040
Subjects with at least one TEAE	667 (17.7%)	597 (14.8%)
Eye Disorders	**9 (0.2%)**	**14 (0.3%)**
Ocular hyperemia	0	10 (0.25%)
Gastrointestinal Disorders	**73 (1.9%)**	**97 (2.4%)**

Diarrhea	4 (0.1%)	12 (0.3%)
Nausea	12 (0.3%)	26 (0.6%)
Vomiting	10 (0.3%)	34 (0.8%)
General Disorders	**42 (1.1%)**	**147 (3.6%)**
Asthenia	1 (0.02%)	15 (0.4%)
Chills	2 (0.05%)	18 (0.45%)
Fatigue	16 (0.4%)	28 (0.7%)
Flu-like illness	3 (0.1%)	45 (1.1%)
Pyrexia	4 (0.1%)	37 (0.9%)
Hepatobiliary Disorders	**119 (3.2%)**	**30 (0.7%)**
Hepatotoxicity	113 (3.0%)	24 (0.6%)
Immune System Disorders	**6 (0.15%)**	**26 (0.6%)**
Hypersensitivity	3 (0.1%)	19 (0.5%)
Drug hypersensitivity	0	4 (0.1%)
Injury/Poisoning	**160 (4.3%)**	**300 (7.4%)**
Incorrect dose	26 (0.7%)	15 (0.4%)
Toxicity to various agents	85 (2.3%)	258 (6.3%)
Musculoskeletal Disorders	**51 (1.3%)**	**58 (1.4%)**
Arthralgia	4 (0.1%)	12 (0.3%)
Myalgia	2 (0.05%)	24 (0.6%)
Nervous System Disorders	**45 (1.2%)**	**86 (2.1%)**
Headache	22 (0.6%)	62 (1.5%)
Pregnancy/Puerperium/Perinatal	**72 (1.9%)**	**45 (1.1%)**
Pregnancy	71 (1.9%)	45 (1.1%)
Respiratory Disorders	**113 (3.0%)**	**65 (1.6%)**
Bronchitis	20 (0.5%)	5 (0.1%)
Dyspnea	8 (0.2%)	13 (0.3%)
Skin and SC Disorders	**72 (1.9%)**	**90 (2.2%)**
Rash	18 (0.5%)	24 (0.6%)
Rash macular	1 (0.02%)	2 (0.05%)
Rash pruritic	13 (0.3%)	16 (0.4%)
Rash generalized	0	2 (0.05%)
Urticaria	6 (0.15%)	14 (0.4%)
Vascular Disorders	**46 (1.2%)**	**66 (1.6%)**
Dizziness	11 (0.3%)	30 (0.8%)

Reviewer's Comments
Differences in coding resulted in different frequency of AE codes in several organ systems. A significantly higher proportion of subjects in the 9INH arm had a hepatic AE, while a significantly higher proportion of subjects in the 3RPT/INH arm experienced a pre-defined syndrome of hypersensitivity reaction. The latter is manifested with a higher proportion of

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subjects who experienced fever, nausea, vomiting, fatigue, flu-like illness, arthralgias, myalgias, ocular hyperemia, headache, rash and dizziness in the 3RPT/INH arm.

This study did not report whether subjects who had hepatic AEs experienced clinical symptoms of hepatitis. Liver enzymes were only measured for the first 644 subjects enrolled and for subjects considered at high risk for liver injury, including those with history of alcohol use or hepatitis B or C or HIV infection. The frequency of hepatitis in the 9INH arm in this study (3.0%) is higher than what is reported in the previously cited Cochrane Review[3] (hepatotoxicity associated with 6 months and 12 months of INH occurred in 0.36% and 0.52% of recipients in the studies analyzed) and higher than what is included in INH product labeling (23/1000 highest risk, occurring in persons 50-64 years of age). The difference is most likely due to the inclusion of HIV infected subjects in this study (see AE of Special Interest) and monitoring hepatotoxicity preferentially in patients at risk for liver injury whereas the studies analyzed in the Cochrane review were conducted in HIV negative patients and INH labeling likely predated HIV infection era.

The higher number of pregnancies in the 9INH arm reflects the longer duration of treatment.

Overall, there were no new AEs that are not already included in the product labeling of either RPT or INH. However, the currently approved Priftin label does not describe the signs and symptoms of hypersensitivity and only includes hypersensitivity in the Contraindications section but not in the Warnings section. Labeling will be updated with information regarding hypersensitivity.

Table 59: Summary of AEs by Age TBTC Study 26 Main Study – Applicant Dataset

	9INH				3RPT/INH			
	<18 y	**18-64 y**	**≥65 y**	**Total**	**<18 y**	**18-64 y**	**≥65 y**	**Total**
N	342	3294	123	3759	348	3537	155	4040
AE	29 (8.2%)	610 (18.5%)	28 (22.0%)	667 (17.7%)	27 (7.8%)	540 (15.2%)	30 (18.7%)	597 (14.8%)
Treatment related AE	2 (0.6%)	214 (6.5%)	9 (6.5%)	225 (6.0%)	10 (2.9%)	321 (9.1%)	21 (13.5%)	352 (8.7%)
D/C due to AE	2 (0.6%)	135 (4.1%)	5 (4.1%)	142 (3.8%)	5 (1.4%)	179 (5.1%)	12 (7.7%)	196 (4.9%)
SAE	4 (1.2%)	99 (3.0%)	9 (6.5%)	112 (3.0%)	0 0%	57 (1.6%)	8 (5.2%)	65 (1.6%)
Treatment related SAE	0	7 (0.2%	0	7 (0.2%)	0	10 (0.3%)	4 (2.6%)	14 (0.3%)
Died	2 (0.6%)	31 (0.9%)	7 (5.7%)	40 (1.0%)	0	21 (0.6%)	10 (6.5%)	31 (0.8%)

Table 60: Summary of AEs by Sex – Study 26 Main – Applicant Dataset

	9INH			3RPT/INH		
	M	F	Total	M	F	Total
N	2013	1746	3759	2242	1798	4040
AE	275 (13.7%)	392 (22.5%)	667 (17.7%)	265 (11.7%)	332 (18.5%)	597 (14.8%)
Treatment Related AE	91 (4.5%)	134 (7.7%)	225 (6.0%)	157 (7.0%)	195 (10.8%)	352 (8.7%)
D/C due to Treatment Related AE	59 (2.9%)	83 (4.8%)	142 (3.8%)	91 (4.1%)	105 (5.8%)	196 (4.9%)
SAE	63 (3.0%)	49 (2.8%)	112 (3.0%)	40 (1.8%)	25 (1.3%)	65 (1.6%)
Treatment Related SAE	3 (0.1%)	4 (0.2%)	7 (0.2%)	8 (0.3%)	6 (0.3%)	13 (0.3%)
Died	29 (1.4%)	11 (0.6%)	40 (1.0%)	22 (1.0%)	9 (0.5%)	31 (0.8%)

Table 61: Summary of AEs by Race – Study 26 Main – Applicant Dataset

	9INH				3RPT/INH			
	White	Black	Other	Total	White	Black	Other	Total
N	2184	935	640	3759	2343	981	716	4040
AE	384 (17.5%)	183 (19.3%)	100 (15.5%)	667 (17.7%)	348 (14.8%)	136 (13.9%)	113 (15.6%)	597 (14.8%)
Treatment Related AE	148 (6.8%)	38 (3.6%)	39 (6.1%)	225 (6.0%)	217 (9.3%)	66 (6.7%)	69 (9.6%)	352 (8.2%)
D/C due to Treatment Related AE	92 (4.2%)	20 (2.1%)	30 (4.7%)	142 (3.8%)	122 (5.2%)	33 (3.4%)	41 (5.7%)	196 (4.8%)
SAE	57 (2.5%)	41 (4.3%)	14 (2.2%)	112 (3.0%)	28 (1.2%)	27 (2.8%)	10 (1.4%)	65 (1.6%)
Treatment Related AE	6 (0.2%)	0	1 (0.2%)	7 (0.2%)	6 (0.2%)	5 (0.5%)	3 (0.4%)	14 (0.3%)
Died	16 (0.7%)	19 (2.0%)	5 (0.8%)	40 (1.0%)	18 (0.8%)	10 (1.0%)	3 (0.4%)	31 (0.8%)

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Table 62: Summary of AEs by Study Site and Country of Enrollment – TBTC Study 26 Main – Applicant Dataset

	9INH N = 3759	3RPT/INH N = 4040
Any AE	667 (17.7%)	597 (14.8%)
Study Site		
12	3/13 (23.1%)	3/20 (15.0%)
13	26/176 (14.8%)	8/177 (4.5%)
14	15/115 (13.0%)	11/103 (10.7%)
15	15/66 (22.7%)	9/58 (15.5%)
16	5/120 (4.2%)	4/180 (2.2%)
17	26/152 (17.1%)	14/201 (7.0%)
20	98/685 (14.2%)	107/688 (15.6%)
21	11/39 (28.2%)	11/48 (20.8%)
22	45/163 (27.6%)	30/169 (17.8%)
23	18/86 (20.9%)	8/89 (7.9%)
24	33/152 (21.0%)	22/190 (11.6%)
25	24/140 (16.4%)	25/136 (18.4%)
26	40/92 (43.5%)	52/156 (33.3%)
27	6/53 (11.3%)	12/63 (19.0%)
28	17/115 (14.8%)	14/100 (14.0%)
29	33/315 (10.2%)	35/323 (10.8%)
31	12/100 (12.0%)	10/147 (6.8%)
40	38/305 (12.5%)	44/329 (13.4%)
53	15/22 (68.2%)	11/23 (47.8%)
54	59/99 (59.6%)	36/96 (37.5%)
58	11/58 (19.0%)	9/55 (16.4%)
59	8/74 (10.8%)	23/100 (23.0%)
61	4/64 (6.3%)	5/55 (9.1%)
62	4/32 (12.5%)	4/28 (14.3%)
63	27/253 (10.7%)	34/250 (13.6%)
66	17/82 (20.7%)	10/74 (13.5%)
68	0/0	0/1
70	57/188 (30.9%)	46/181 (25.4%)
Brazil/Spain	45/415 (10.8%)	45/470 (9.6%)
US/Canada	622/3344 (18.6%)	552/3570 (15.5%)

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Reviewer's Comments
In both treatment arms, AEs, SAEs, treatment related AEs and treatment related SAEs occurred less frequently in children <18 years of age compared to adults, and more frequently in subjects above the age of 65 compared to younger adults.

In both treatment arms, AEs and treatment related AEs occurred more frequently in females compared to males, but deaths were more frequent in males.

In both treatment arms, deaths and SAEs occurred in a higher proportion of black subjects compared to white subjects.

The frequency of reported AEs varied greatly by study site, but overall, the pattern of AEs within each site was similar to the overall pattern in the study. Sites in the US/Canada reported AEs more frequently compared to sites in Brazil/Spain.

Table 63: Treatment Emergent AEs Occurring in ≥0.5% of Subjects – Pediatric Substudy - Legacy

	9INH N = 493	3RPT/INH N = 539
Any AE	**63 (12.8%)**	**52 (9.6%)**
Blood and Lymphatic Disorders	**4 (0.8%)**	**1 (0.2%)**
Lymphadenopathy	3 (0.6%)	0
Immune Disorders	**1 (0.2%)**	**8 (1.5%)**
Hypersensitivity	0	7 (1.3%)
Infections and Infestations	**30 (6.0%)**	**19 (3.5%)**
Impetigo	3 (0.6%)	0
Influenza	0	2 (0.4%)
Otitis media	5 (1.0%)	0
Strep pharyngitis	3 (0.6%)	0
URI	2 (0.4%)	3 (0.6%)
Injury/Poisoning	**18 (3.7%)**	**10 (1.8%)**
Medication error	13 (2.6%)	8 (1.5%)
Pregnancy	**5 (1.0%)**	**2 (0.4%)**

Pregnancy	5 (1.0%)	2 (0.4%)
Skin Disorders	**6 (1.2%)**	**6 (1.2%)**
Skin reaction	1 (0.2%)	3 (0.6%)
Rash	3 (0.6%)	1 (0.2%)

Table 64: Treatment Emergent AEs Occurring in ≥0.5% of Subjects – Pediatric Substudy – Applicant Dataset

	9INH N = 493	3RPT/INH N = 539
Any AE	**63 (12.8%)**	**52 (9.6%)**
Blood and Lymphatics	**4 (0.8%)**	**1 (0.2%)**
Lymphadenopathy	3 (0.6%)	0
General Disorders	**2 (0.4%)**	**5 (0.9%)**
Flu like illness	0	3 (0.6%)
Infection and Infestations	**23 (%)**	**12 (2.2%)**
Otitis media	5 (1.0%)	1 (0.2%)
Impetigo	3 (0.6%)	0
URI	2 (0.4%)	1 (0.2%)
Injury/Poisoning	**15 (3.0%)**	**15 (2.8%)**
Incorrect dose	11 (2.2%)	8 (1.5%)
Toxicity to various agents	0	6 (1.2%)
Pregnancy	**5 (1.0%)**	**2 (0.4%)**
Pregnancy	5 (1.0%)	2 (0.4%)
Skin Disorders	**8 (1.6%)**	**8 (1.5%)**
Rash	3 (0.6%)	3 (0.6%)

Reviewer's Comments
The proportion of subjects experiencing at least one AE was higher in the 2-11 age group compared to the 12-17 age group (see Summary of AEs, pediatric substudy, table 47), but the overall pattern of AEs was similar (except obviously pregnancy). There were no cases of hepatotoxicity/hepatitis reported in either treatment arm. All cases of hypersensitivity reactions were reported in the 3RPT/INH arm.

Table 65: Treatment Emergent AE Occurring in ≥1% - HIV Substudy - Legacy

	9INH N = 186	3RPT/INH N = 207
Any TEAE	75 (40.3%)	45 (21.7%)
Blood and Lymphatics	**8 (4.3%)**	**3 (1.5%)**
Anemia	5 (2.7%)	0
Gastrointestinal Disorders	**20 (10.8%)**	**6 (2.9%)**
Diarrhea	6 (3.2%)	4 (1.9%)
Gastritis	5 (2.7%)	0
Hepatobiliary Disorders	**14 (7.5%)**	**5 (2.4%)**
Hepatitis	13 (7.0%)	3 (1.5%)
Infections and Infestations	**40 (21.5%)**	**20 (9.7%)**
Acrodermatitis	3 (1.6%)	1 (0.5%)
Anogenital warts	4 (2.1%)	1 (0.5%)
Bronchitis	3 (1.6%)	2 (1.0%)
Genital herpes	4 (2.1%)	3 (1.5%)
Herpes zoster	5 (2.7%)	1 (0.5%)
UTI	3 (1.6%)	0
Tonsillitis	3 (1.6%)	1 (0.5%)
Nasopharyngitis	8 (4.3%)	3 (1.5%)
URI	2 (1.1%)	0
Vaginitis	2 (1.1%)	0
Musculoskeletal Disorders	**2 (1.1%)**	**4 (1.9%)**
Back pain	2 (1.1%)	0
Nervous System Disorders	**4 (2.1%)**	**4 (1.9%)**
Headache	2 (1.1%)	1 (0.5%)
Psychiatric Disorders	**5 (2.7%)**	**4 (1.9%)**
Depression	1 (0.5%)	3 (1.5%)
Suicide attempt	2 (1.1%)	0
Skin/SC Disorders	**7 (3.8%)**	**3 (1.5%)**
Dermatitis	2 (1.1%)	0

Table 66: Treatment Emergent AE Occurring in ≥1% of Subjects – HIV Substudy – Applicant Dataset

	9INH N = 186	3RPT/INH N = 207
Any TEAE	**75 (40.3%)**	**45 (21.7%)**
Blood and Lymphatics	**7 (3.8%)**	**4 (1.9%)**
Anemia	4 (2.1%)	0
Neutropenia	1 (0.5%)	3 (1.5%)
Gastrointestinal Disorders	**18 (9.7%)**	**6 (2.9%)**
Diarrhea	6 (3.2%)	4 (1.9%)
Gastritis	5 (2.7%)	0
Hepatobiliary Disorders	**16 (8.6%)**	**6 (2.9%)**
Hepatotoxicity	14 (7.5%)	3 (1.5%)
Infections and Infestations	**24 (12.9%)**	**13 (6.3%)**
Anogenital warts	4 (2.1%)	1 (0.5%)
Genital herpes	4 (2.1%)	3 (1.5%)
Injury/Poisoning	**5 (2.7%)**	**6 (2.9%)**
Toxicity to various agents	0	3 (1.5%)
Psychiatric Disorders	**6 (3.2%)**	**4 (1.9%)**
Depression	1 (0.5%)	3 (1.5%)
Suicide attempt	2 (1.1%)	0
Respiratory Disorders	**15 (8.1%)**	**5 (2.4%)**
Bronchitis	3 (1.6%)	1 (0.5%)
Nasopharyngitis	6 (3.2%)	2 (1.0%)
Skin Disorders	**15 (8.1%)**	**7 (3.4%)**
Acrodermatitis	3 (1.6%)	2 (1.0%)
Dermatitis	2 (1.1%)	1 (0.5%)
Herpes Zoster	3 (1.6%)	1 (1.5%)

Reviewer' Comments
Similar to the main study, there were discrepancies in coding between the two datasets. For example, bronchitis was coded under Infections and Infestations SOC in the legacy dataset and under Respiratory Disorders SOC in the converted data. HSV and Zoster infections were under Infections SOC in the legacy dataset and under Skin in the converted dataset. Tonsillitis was under both Respiratory and Infection in the converted data.

The frequency of hepatitis in either treatment arm in the HIV infected population was approximately twice the rate in the overall population in Study 26. The frequency of hypersensitivity reactions in the HIV population was considerably lower compared to the main Study 26; only one subject was reported as having a rifamycin hypersensitivity reaction, a 40

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year old woman. One pregnancy occurred in the INH arm. This subject was not enrolled in the main study and the outcome was not reported.

Treatment Related AEs
Relatedness of the AE to study treatment was determined by the investigator and was classified as definite, probable, possible, unlikely, unrelated or unknown in the legacy dataset, and re-classified as related or not related in the datasets converted to conform to CDISC standards.

Table 67: Treatment Related Treatment Emergent AEs Occurring in ≥0.5% – TBTC 26 Main – Legacy Data

	9INH N = 3759	3RPT/INH N = 4040
Immune System Disorders	18	160
Hypersensitivity	18 (0.5%)	160 (4.0%)
Hepatobiliary Disorders	103	19
Hepatitis	103 (2.7%)	18 (0.5%)

Table 68: Treatment Related Treatment Emergent AEs – TBTC 26 Main – Applicant Data

MedDRA v. 14.0 System Organ Class Preferred Term	9INH N = 3759	3RPT/INH N = 4040
Treatment related AE	225 (6.0%)	352 (8.7%)
Eye Disorders	**1 (0.02%)**	**10 (0.25%)**
Ocular hyperemia	0	10 (0.25%)
Gatrointestinal Disorders	**25 (0.7%)**	**78 (1.9%)**
Diarrhea	2 (0.05%)	8 (0.2%)
Nausea	8 (0.2%)	26 (0.6%)
Vomiting	4 (0.1%)	31 (0.77%)
General Disorders	**24 (0.6%)**	**133 (3.3%)**
Asthenia	1 (0.02%)	13 (0.3%)
Chills	2 (0.05%)	16 (0.4%)
Fatigue	13 (0.3%)	27 (0.7%)
Flu-like Illness	1 (0.02%)	38 (0.9%)
Pyrexia	1 (0.02%)	35 (0.9%)
Hepatobiliary Disorders	**107 (2.8%)**	**24 (0.6%)**
Hepatotoxicity	107 (2.8%)	24 (0.6%)
Immune System Disorders	**2 (0.05%)**	**21 (0.5%)**
Hypersensitivity	2 (0.05%)	21 (0.5%)

Injury/Poisoning	**85 (2.3%)**	**258 (6.3%)**
Toxicity to various agents	85 (2.3%)	258 (6.3%)
Musculoskeletal Disorders	**13 (0.3%)**	**35 (0.9%)**
Arthralgia	4 (0.1%)	9 (0.2%)
Myalgia	2 (0.05%)	23 (0.6%)
Nervous System Disorders	**32 (0.85%)**	**62 (1.5%)**
Headache	17 (0.5%)	50 (1.2%)
Skin/SC Tissue Disorders	**38 (1.0%)**	**70 (1.7%)**
Rash	15 (0.4%)	24 (0.6%)
Rash macular	1 (0.02%)	1 (0.02%)
Rash pruritic	9 (0.24%)	14 (0.4%)
Urticaria	4 (0.1%)	13 (0.4%)
Vascular Disorders	**9 (0.2%)**	**35 (0.9%)**
Dizziness	9 (0.2%)	30 (0.8%)

Reviewer's Comments
A significantly higher percentage of subjects developed treatment related hepatitis in the 9INH arm while a significantly higher percentage of 3RPT/INH recipients developed treatment related hypersensitivity reaction.
Treatment related AEs that led to treatment discontinuation were detailed under the Discontinuations section 7.3.3. These were mainly hepatitis in the 9INH arm and symptoms of hypersensitivity in the 3RPT/INH arm.

In the pediatric substudy, the applicant dataset indicated that six (1.2%) subjects in the 9INH arm had AEs that were considered to be treatment related: adenopathy (2), hepatomegaly (1), rash (2), asthenia (1) and dysuria (1). Fifteen (2.8%) subjects in the 3RPT arm had AEs that were considered treatment related: drug intolerance, dyspnea, fatigue, headache, flu-like illness, lip blister, nausea, neutropenia, rash, toxicity to various agents, urticaria and vomiting.

In the legacy dataset, three 9INH subjects and eight 3RPT/INH subjects had an AE that was definitely, probably or possibly treatment related: adenopathy (2) and hepatomegaly in the 9INH arm and hypersensitivity (7), and flu-like illness with neutropenia (1).

In the HIV substudy, twenty one 9INH (11.3%) subjects experienced an AE that was judged to be drug related: hepatotoxicity (12), drug toxicity (1), gastritis (5), dyspepsia (1), dermatitis (1), and anemia (1).
Fifteen 3RPT/INH subjects (7.2%) experienced an AE that was judged to be drug related: hepatotoxicity (3), drug toxicity (2), increased ALT (1), confusion (1), depression (1), dyspepsia (1), gastrointestinal infection (1), gout (1), myositis (1), nausea (1), pyrexia (1) and rash (1). In one subject, the drug toxicity was a hypersensitivity reaction manifesting as cough, chills and headache.

7.3.5 Submission Specific Primary Safety Concerns

The AEs of primary concern are hepatic and hypersensitivity reactions.

Hepatotoxicity was defined as AST≥3xULN in the presence of specific signs and symptoms of hepatitis, or AST>5xULN regardless of signs or symptoms.

In the main study, hepatotoxicity developed in 113 9INH recipients (3%). The majority were assessed as drug related (107/113 in the converted dataset, 103/113 in the legacy dataset). In the 3RPT/INH arm, 24 subjects had hepatotoxicity, all assessed as treatment related.

Outcome of hepatotoxicity was indicated as unresolved/not recovered for six (6/24, 25%) 3RPT/INH subjects and fifty (50/113, 44.3%) 9INH subjects. 4 subjects were hospitalized due to hepatotoxicity, 3 in the 9INH arm, one in the 3RPT arm. No subject required liver transplantation or died due to hepatic toxicity.

Table 69: Subjects with Hepatotoxicity – TBTC 26 Study Main

	9INH N = 3759	**3RPT/INH N = 4040**
Hepatotoxicity	113 (3.0%)	24 (0.6%)
Grade 3	74 (2.0%)	18 (0.5%)
Grade 4	12 (0.4%)	3 (0.08%)
Median age	45 (21-85)	45 (19-72)
≥65 years ≥18-64 years 12-17 years 2-11 years	4/123 (3.3%) 109/3294 (3.3%) 0/262 0/80	2/155 (1.3%) 22/3537 (0.6%) 0/244 0/104
M F	54/2013 (2.6%) 59/1746 (3.4%)	14/2242 (0.6%) 10/1798 (0.6%)
White Black Asian/Pacific Islander American Indian Other	79/2184 (3.6%) 16/935 (1.7%) 9/489 (1.8%) 2/33 (6.1%) 7/118 (6.0%)	13/2343 (0.6%) 6/981 (0.6%) 0/493 3/83 (3.6%) 2/140 (1.4%)
Doses taken <25% (68 doses) 25-<50 (69-134 doses) 50-<75 (135-203 doses) ≥ 75% (≥204 doses)	 31/407 (7.6%) 36/232 (15.5%) 15/213 (7.0%) 31/2907 (1.1%)	
Doses taken <25% (<3 doses)		1/175 (0.6%)

25-<50 (3-5 doses) 50-<75 (6-8 doses) ≥ 75% (≥9 doses)		9/255 (3.5%) 5/143 (3.5%) 9/3467 (0.3%)
HIV positive HIV negative HIV unknown	6/95 (6.3%) 52/1760 (3.0%) 55/1904 (2.9%)	3/105 (2.9%) 12/1775 (0.7%) 9/2160 (0.4%)
HCV positive HCV negative HCV unknown	13/93 (14.0%) 99/3631 (2.7%) 1/35 (2.8%)	4/95 (4.2%) 20/1775 (1.1%) 0/2160
HBV positive Negative Unknown	7/59 (11.9%) 105/3661 (2.9%) 1/39 (2.6%)	0/40 24/3955 (0.6% 0/45
History of ETOH No Unknown	66/1879 (3.5%) 47/1876 (2.5%) 0/4	16/1945 (0.8%) 8/2091 (0.4%) 0/4
USA/Canada Brazil/Spain	106/3344 (3.2%) 7/415 (1.7%)	23/3570 (0.6%) 1/470 (0.2%)
Study site		
12	1/13 (7.7%)	0/20
13	5/176 (2.8%)	0/177
14	5/115 (4.3%)	2/103 (1.9%)
15	2/66 (3.0%)	1/58 (1.7%)
16	1/120 (0.8%)	1/180 (0.6%)
17	3/152 (2.0%)	1/201 (0.5%)
20	19/685 (2.8%)	5/688 (0.7%)
21	5/39 (12.8%)	2/48 (4.2%)
22	7/163 (4.3%)	3/169 (1.8%)
23	5/86 (5.8%)	0/89
24	5/152 (3.3%)	0/190
25	10/140 (7.1%)	0/136
26	5/92 (5.4%)	2/156 (1.3%)
27	2/53 (3.8%)	0/63
28	0/115	0/100
29	1/315 (0.3%)	0/323
31	6/100 (6.0%)	1/147 (0.7%)
40	6/305 (2.0%)	0/329
53	2/22 (9.1%)	1/23 (4.3%)
54	5/99 (5.0%)	0/96
58	0/58	0/55
59	3/74 (4.0%)	1/100 (1.0%)
61	0/64	1/55 (1.8%)

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62	0/32	0/28
63	5/253 (2.0%)	1/250 (0.4%)
66	2/82 (2.4%)	1/74 (1.4%)
70	8/188 (4.3%)	1/181 (0.6%)

Reviewer's Comments
All the subjects who developed hepatotoxicity were adults; no cases were reported in children <18 years of age. INH labeling indicates that the risk of hepatotoxicity in adults ≥20 years of age is up to 2.3%, with the highest risk in the 50-64 age group. In both treatment arms, frequency of hepatotoxicity was greater in subjects with HBV, HCV or HIV infection, and subjects with history of alcohol use compared to the overall frequency in the study. Rates of hepatotoxicity varied considerably among study sites, and were higher among subjects enrolled in the US/Canada compared to subjects enrolled in Brazil/Spain. There was no apparent correlation between dose and occurrence of hepatotoxicity.

The legacy dataset coded rifamycin hypersensitivity/flu-like syndrome using the following definition: either a) one of the following: hypotension, urticaria, angioedema, acute bronchospasm, or conjunctivitis occurring in relation to study drug or b) at least 4 of the following symptoms occurring in relation to the study drug, with ≥1 symptom being Grade 2 or higher: weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, SOB, flushing or chills. No standardized definition was used for INH hypersensitivity reaction.

One hundred and sixty one (161) subjects in the 3RPT/INH and 18 subjects in the 9INH arm (4.0% vs 0.5%) developed a hypersensitivity reaction which was also described as flu-like illness.

Table 70: Characteristics of Subjects with Hypersensitivity Reaction – TBTC Study 26 Main

	9INH N = 3759	**3RPT/INH N = 4040**
Hypersensitivity	18 (0.5%)	161 (4.0%)
Grade 3	7 (0.2%)	69 (1.7%)
Grade 4	0	9 (0.2%)
Median age	38 (22-68)	39 (14-80)
≥65 ≥18-64 12-17 2-11	1/123 (0.8%) 17/3294 (0.5%) 0/262 0/80	10/155 (6.5%) 146/3537 (4.1%) 5/244 (2.0%) 0/104
F M	17/1746 (1.0%) 1/2013 (0.05%)	90/1798 (5.0%) 71/2242 (3.2%

HIV infected HIV negative HIV unknown	0/95 11/1760 (0.6%) 7/1904 (0.4%)	1/105 (1.0%) 86/1775 (4.8%) 74/2160 (3.4%)
White Black Asian American Indian Other	10/2184 (0.5%) 3/935 (0.3%) 5/489 (1.0%) 0/33 0/118	105/2343 (4.5%) 23/981 (2.3%) 23/493 (4.7%) 6/83 (7.2%) 4/140 (2.9%)
Doses taken <25% (68 doses) 25-<50 (69-134 doses) 50-<75 (135-203 doses) ≥ 75% (≥204 doses)	 14/407 (3.4%) 3/232 (0.9%) 0/213 1/2907 (0.03%)	
Doses taken <25% (<3 doses) 25-<50 (3-5 doses) 50-<75 (6-8 doses) ≥ 75% (≥9 doses)		 22/175 (12.6%) 79/255 (31.0%) 33/143 (23.1%) 27/3467 (0.8%)
US/Canada Brazil/Spain	16/3344 (0.5%) 2/415 (0.5%)	153/3570 (4.3%) 8/470 (1.7%)
Study site		
12	0/13	0/20
13	0/176	0/177
14	0/115	1/103 (1.0%)
15	0/66	0/58
16	0/120	0/180
17	0/152	2/201 (0.5%)
20	6/685 (0.9%)	27/688 (3.9%)
21	1/39 (2.6%)	8/48 (16.7%)
22	2/163 (1.2%)	9/169 (5.3%)
23	0/86	2/89 (2.2%)
24	2/152 (1.3%)	4/190 (2.1%)
25	0/140	9/136 (6.6%)
26	2/92 (2.2%)	19/156 (12.2%)
27	0/53	7/63 (11.1%)
28	2/115 (0.2%)	0/100
29	1/315 (0.3%)	9/323 (2.8%)
31	1/100 (1.0%)	1/147 (0.7%)
40	0/305	9/329 (2.7%)
53	0/22	4/23 (17.4%)
54	0/99	8/96 (8.3%)

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58	0/58	2/55 (3.6%)
59	0/74	6/100 (6.0%)
61	0/64	3/55 (5.5%)
62	0/32	1/28 (3.6%)
63	1/253 (0.4%)	18/250 (7.2%)
66	0/82	2/74 (2.7%)
70	0/188	10/181 (5.5%)

Reviewer's Comments
Rifamycin hypersensitivity reaction/flu-like syndrome occurred more frequently in women, HIV negative (or unknown) subjects and adults. No cases were reported in children 2-11 years of age and only one case occurred in HIV infected individuals. The median dose received prior to onset of symptoms was 4. Rates of rifamycin hypersensitivity varied considerably between study sites, and were reported more frequently in the US/Canada than in Brazil/Spain.

There was no definition for INH hypersensitivity. In general, INH hypersensitivity may manifest with fever, skin eruptions, lymphadenopathy and vasculitis. The symptoms coded as INH hypersensitivity included a combination of fever, rash, diarrhea, fatigue, chills and body aches. These reactions occurred predominantly in women, adults and HIV negative individuals.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Please refer to section 7.3.4.

7.4.2 Laboratory Findings

Serum laboratory tests were performed at baseline within 60 days of enrollment for the first 322 subjects randomized to each treatment arm, and on HIV-infected subjects and subjects with known liver disease or at risk for liver disease (self-reported alcohol abuse, injection drug use, viral hepatitis, cirrhosis, or women <3 months postpartum) . Tests included AST, ALT, total bilirubin, alkaline phosphatase, creatinine, hematocrit, hemoglobin, and CBC with platelets. If elevated at baseline, AST was repeated in a month.

The tabulations of elevated lab values were derived from the lb dataset.

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Table 71: Laboratory Values – TBTC Study 26 Main

	9INH	3RPT/INH
ALT >3-5xULN		
Baseline	8/2032 (0.4%)	15/2155 (0.7%)
1 month	18/890 (2.0%)	18/1152 (1.5%)
Treatment	113/1395 (8.1%)	33/1331 (2.5%)
ALT >5-10xULN		
Baseline	0/2032	0/2155
1 month	13/890 (1.5%)	8/1152 (0.7%)
Treatment	60/1395 (4.3%)	13/1331 (1.0%)
ALT >10xULN		
Baseline	0/2032	0/890
1 month	5/890 (0.6%)	4/1152 (0.3%)
Treatment	29/1395 (2.1%)	12/1331 (0.9%)
AST >3-5xULN		
Baseline	9/2912 (0.3%)	8/2730 (0.3%)
1 month	20/1038 (1.9%)	17/1304 (1.3%)
Treatment	92/1530 (6.0%)	35/1495 (2.3%)
AST >5-10xULN		
Baseline	0/2912	1/2730 (0.03%)
1 month	10/1038 (1.0%)	11/1304 (0.8%)
Treatment	44/1530 (2.9%)	12/1495 (0.8%)
AST >10xULN		
Baseline	0/2912	0/2730
1 month	3/1038 (0.3%)	2/1304 (0.2%)
Treatment	19/1530 (1.2%)	4/1495 (0.3%)
Bilirubin >1.5xULN		
Baseline	35/2645 (1.3%)	17/2805 (0.6%)
1 month	10/969 (1.0%)	23/1246 (1.8%)
Treatment	40/1456 (2.7%)	32/1436 (2.2%)
Alkaline Phosphatase >2.5xULN		
Baseline	4/2021 (0.2%)	6/2146 (0.3%)
1 month	59/872 (6.8%)	73/1126 (0.06%)
Treatment	4/1364 (0.3%)	7/1300 (0.5%)
Creatinine >1.5xULN		
Baseline	15/1825 (0.8%)	22/1958 (1.1%)
1 month	11/931 (1.2%)	16/985 (1.6%)
Treatment	20/1146 (1.7%)	23/1166 (2.0%)
Hemoglobin < 8 g/dL		
Baseline	31/2139 (1.5%)	32/2240 (1.4%)

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1 month	16/423 (3.8%)	26/771 (3.3%)
Treatment	79/771 (10.2%)	55/954 (5.8%)
WBC<2000 cells/mm^3		
Baseline	0/2139	3/2239 (0.1%)
1 month	1/423 (0.2%)	3/769 (0.4%)
Treatment	2/769 (0.2%)	3/952 (0.3%)
Platelets <75000/mm^3		
Baseline	0/2129	2/2232 (0.09%)
1 month	1/417 (0.2%)	2/767 (0.3%)
Treatment	6/761 (0.8%)	4/951 (0.42%)

Reviewer's Comments
Of the 137 subjects indicated as having hepatotoxicity (113 9INH and 24 3RPT/INH), 126 (104 in the INH arm and 22 in the 3RPT arm) had ALT or AST > 3x ULN post-baseline. The remaining subjects had levels that were >ULN but <3xULN, but with >3x change compared to baseline.

Twenty subjects, 10 in the 9INH arm and 10 in the RPT/INH arm had lab values that satisfied Hy's law during the first month or the treatment period. The outcome was indicated as not recovered for 3 subjects in the INH arm (0852, 2603 and 4171) and two subjects in the 3RPT/INH arm (Subjects 2907 and 0764).

Anemia with Hb<8 developed more frequently in the INH arm; otherwise, there were no significant differences in the proportion of subjects who had hematologic abnormalities or Cr elevations.

Table 72: Laboratory Values – Pediatric Substudy

	9INH	3RPT/INH
ALT >3xULN		
Baseline	2/93 (2.2%)	4/63 (6.3%)
Month 1 or Treatment	1/50 (2.0%)	0/37
AST >3x ULN		
Baseline	8/140 (5.7%)	11/113 (9.7%)
Month 1 or Treatment	1/60 (1.7%)	0/44
Bilirubin >1.5xULN		
Baseline	9/138 (6.5%)	1/107 (0.9%)
Month 1 or Treatment	3/57 (5.3%)	3/40 (7.5%)

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No patient in either arm had liver tests that satisfied Hy's law.

Table 73: Laboratory Values –HIV substudy

	9INH	3RPT/INH
ALT >3-5xULN		
Baseline	1/135 (0.7%)	2/152 (1.3%)
Month 1 or Treatment	16/125 (12.8%)	4/141 (2.8%)
ALT >5x ULN		
Month 1 or Treatment	10/125 (8.0%)	3/141 (2.1%)
AST >3xULN		
Baseline	0/190 (0)	1/203 (0.5%)
Month 1 or Treatment	14/155 (9.0%)	10/174 (5.7%)
AST >5xULN		
Month 1 or Treatment	8/155 (5.2%)	3/174 (1.7%)
Bilirubin >1.5xULN		
Baseline	1/175 (0.6%)	4/189 (2.1%)
Month 1 or Treatment	9/155 (5.8%)	15/172 (8.7%)
Hb <8		
Baseline	2/170 (1.2%)	8/186 (4.3%)
Month 1 or Treatment	7/147 (4.8%)	8/163 (4.9%)

Two subjects in each arm had liver enzyme pattern that satisfied Hy's law during treatment phase. Both subjects were enrolled in the main study. The outcome was indicated as not resolved for one subject in each arm (Subject 4171 in the 9INH arm and Subject 0764 in the 3RPT/INH arm).

7.4.3 Vital Signs

Vital signs were not obtained during the clinical trials.

7.4.4 Electrocardiograms (ECGs)

ECGs were not obtained during the clinical trials

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7.5 Additional Safety Evaluations

7.5.1 Pregnancy Data

One hundred sixteen subjects became pregnant during the treatment period or within 60 days of the last dose, 71 in the INH arm and 45 in the 3RPT/INH arm.

Table 74: Pregnancy Outcomes Study 26 Main

	9INH N = 3759	3RPT/INH N = 4040
Pregnancies	71	45
Elective abortion	6 (8.5%)	6 (13.3%)*
Spontaneous abortion	9 (12.7%)	7 (15.6%)**
Unknown outcome	2 (2.8%)	2 (4.4%)
Live birth	54 (76.0%)	31 (68.%)
Baby outcome		
Well baby	26	21
Unspecified	26	10
With congenital anomalies	2¥	0

*1/6 of elective abortions in 3RPT/INH arm followed diagnosis of Turner's syndrome
**1/7 spontaneous abortions in 3RPT/INH arm was a non-viable female fetus with a large cystic mass on the neck and Downs syndrome
¥Congenital anomalies: cleft lip, cleft palate and heart abnormality (1), pyloric stenosis (1)

In the Martinson study, 4 subjects in the 3RPT/INH arm became pregnant during the treatment period. One had normal delivery of a live baby, two had elective abortions and one was lost to follow up.

Fourteen (14) cases of pregnancy occurring during rifapentine intake were reported to Sanofi as of December 1, 2013. Four (4/14, 29%) had first-trimester spontaneous abortion. Six healthy babies were born with no reported malformations.

Reviewer's Comments
Rifabutin is pregnancy category (b) (4) *Priftin product labeling states that RPT produced fetal harm and was teratogenic in animal reproduction studies. Increased number of ribs, delayed ossification, cleft palate and right aortic arch were noted in the off-spring of pregnant rats exposed to 0.6x the human dose. At 0.3-1.3x the human dose, major malformations were noted in rabbits, including ovarian agenesis, arhinia, microphthalmia and irregularities of the ossified facial tissue. At higher doses, there were stillborn pups. Labeling also states tha*(b) (4)

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(b) (4)

The risk-benefit considerations for Priftin in the treatment of active TB and the treatment of LTBI are different. Active TB may be fatal if untreated and is transmitted person to person, whereas the goal of treatment of latent TB is prevention of future development of active disease, and latent TB infection is not transmissible. Treatment of active TB is beneficial to the patient and to public health. The benefit of using rifapentine during pregnancy for the treatment of active TB may outweigh the risk, but the benefits of rifapentine in the treatment of latent TB infection may not outweigh risks of potential reproductive complications.

The Division of Pediatric and Maternal Health was consulted for input and labeling recommendations regarding risk of use during pregnancy. The rate of spontaneous abortions noted in patients exposed to rifapentine during pregnancy was thought to be similar to the rate of spontaneous abortions that occur in the general population. Labeling will state that rifapentine can be used in pregnancy if the benefit is determined to outweigh the risk. .

8 Postmarket Experience

Sanofi searched their pharmacovigilance database for the period of 22 June 1998 to 01 December 2013. The search yielded six (6) spontaneous reports and 54 solicited cases involving RPT as suspect drug regardless of indication.

All 6 spontaneous reports originated from health care professionals including 1 literature case. Four were non-serious cases and two were serious: hypersensitivity reaction and fatal respiratory failure. The hypersensitivity reaction occurred in a 49 year-old female after receiving 4 doses of RPT 600 mg once weekly with daily INH. Symptoms included pyrexia, vomiting and body aches and resolved with IV fluids and diphenhydramine. Positive re-challenges were noted with RPT/INH combination then with INH alone. The fatal acute respiratory failure occurred in a 65 year-old male patient on maintenance with hemodialysis, anemia, hypertension and type 2 diabetes. He was receiving INH, ethambutol and rifapentine for the treatment of TB but discontinued after less than 2 months due to numbness in lower limbs and bilateral blurred vision. A few weeks after discontinuing TB treatment, lorazepam was added to citalopram, melitracen, flupentixol, and olanzapine that he was already receiving, with subsequent respiratory failure and death. No autopsy information was provided. This death is not related to rifapentine.

The 54 solicited reports were received from study investigators and included 8 non-serious and 46 serious events, including 12 with fatal outcomes. None of the deaths were assessed by the investigators as related to RPT. Serious AEs mainly pertained to liver injury/hepatotoxicity (9) and hypersensitivity reaction (3). Narratives for the deaths were reviewed. I agree that none was likely to be drug related.

Fourteen (14) cases of pregnancy occurring during rifapentine intake were reported to Sanofi as of December 1, 2013. Four (4/14, 29%) had first-trimester spontaneous abortion. Six healthy babies were born with no reported malformations.

The applicant also conducted a literature search up to December 1, 2013 using Embase database, the terms Priftin, M000473, adverse events, adverse reactions, side effects, tolerance, and tolerability, and the subsearch terms drug-drug interactions, hypersensitivity and hepatotoxicity. The search did not yield results that would require labeling changes pertaining to hepatotoxicity. There were reports of hypersensitivity reactions associated with intermittent exposure or with high doses of other rifamycins, thought to be immunologic in origin. These reactions included thrombocytopenia, hemolytic anemia, renal tubular necrosis, interstitial nephritis, and flu-like syndrome. There were no reports of hypersensitivity reactions specifically associated with rifapentine.

Reviewer's Comment
Priftin labeling contraindicates administration in patients with a history of hypersensitivity but does not describe signs or symptoms associated with such a reaction. Hypersensitivity is (b) (4) *included in the Warnings section.*

A Web of Science search was performed on August 13, 2014 using the term rifapentine. Limiting the search to articles published since1998 (the year rifapentine was approved) yielded 256 publications. One publication described a trial of escalating rifapentine doses in healthy volunteers[13]. This publication reported grade 3 ALT/AST elevations without increase in bilirubin or symptoms in one subject and grade 3 lymphopenia associated with fever, dizziness and elevated liver enzymes in another subject who received 15 mg/kg RPT. There were no other reports specifically reporting hypersensitivity reaction to rifapentine.

The clinical review of the NDA efficacy supplement for Priftin in the treatment of TB submitted in July 2007 and approved in May 2008 that reported the results of TBTC Study 22 did not report hypersensitivity reaction or flu-like illness although the study had pre-specified flu-like illness as an AE of interest. Rifapentine dose was 600 mg once weekly in combination with INH 300 mg daily.

13 Dooley K, Bliven-Sizemore E, et al. Safety and PK of escalating daily doses of the antituberculous drug rifapentine in healthy volunteers. http://www.nature.com/doifinder/doi:10.1038/clpt.2011.323

Reference ID: 3648146

The annual reports submitted to the Priftin NDA did not specifically report hypersensitivity reactions, and did not report drug reactions or rash.

A Phase 1 clinical protocol to evaluate the PK of several doses of rifapentine in healthy subjects conducted under IND 114,790 reported that the study was closed prematurely due to safety concerns: 3/44 subjects experienced drug reaction with eosinophilia syndrome (DRESS), two additional subjects experienced hypersensitivity, and one subject each experienced elevation in ALT and low neutrophil count. The FDA's Office of Surveillance and Epidemiology performed a crude FAERS search for reports of DRESS and/or eosinophilia associated with rifapentine exposure and found no reports. The safety findings were later updated to reclassify DRESS events as hypersensitivity reactions.

The higher incidence of hypersensitivity reactions noted in Study 26 and the study conducted in healthy subjects may be related to the higher doses used (900 mg weekly in Study 26 and 10-15 mg/kg/day in the Phase 1 PK study).

9 Appendices

9.1 Labeling Recommendations

Priftin approved labeling will be changed to PLR format. Labeling updates will be made to the following sections:
Indications and Usage: add the indication of treatment of LTBI
Warnings and Precautions: Add risk of hypersensitivity reactions, re-arrange order of warnings as follows: hepatotoxicity, hypersensitivity, (b) (4) drug-drug interactions, discoloration of body fluids, Clostridium difficile associated diarrhea and porphyria.
Adverse Reactions: add the ARs noted in TBTC Study 26.
Drug-Drug Interactions: Add information regarding interaction of rifapentine and isoniazid, and rifapentine and (b) (4).
Pregnancy: add a risk summary and information regarding spontaneous abortions noted in TBTC Study 26, post-marketing experience and Martinson study.
Pediatrics: Add Information regarding PK studies in children.
Clinical Pharmacology: Update mechanism of action, microbiology and PK sections.
Clinical Studies: Add description of TBTC Study 26 and the pediatric and HIV substudies.

9.2 Advisory Committee Meeting

No advisory committee meeting was held.

9.3 Clinical Investigator Financial Disclosure Review Template

Application Number: 21024 S011
Submission Date(s): May 30, 2014
Applicant: Sanofi-Aventis USA
Product: Priftin® (rifapentine) 150 mg oral tablets

Reviewer: Hala Shamsuddin MD
Date of Review: June 18, 2014
Covered Clinical Study: TBTC Study 26

Was a list of clinical investigators provided:	*Please see Reviewer's Comments*
Total number of investigators identified: >600	
Number of investigators who are sponsor employees (including both full-time and part-time employees): *0*	

Reference ID: 3648146

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): *Not Provided*	
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: *NA* Significant payments of other sorts: *NA* Proprietary interest in the product tested held by investigator: *NA* Significant equity interest held by investigator in sponsor of covered study: *NA*	
Is an attachment provided with details of the disclosable financial interests/arrangements:	*Please see reviewer's comments*
Is a description of the steps taken to minimize potential bias provided:	*Please see reviewer's Comments*
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0	
Is an attachment provided with the reason:	*See Reviewer's Comments*

Reviewer's Comments
TBTC study 26 was a randomized open-label study comparing the effectiveness of 9 month of daily isoniazid to 3 months of weekly isoniazid plus rifapentine in the treatment of latent TB infection. The study was sponsored and conducted by the CDC at 28 study sites, 26 in the US and Canada and one site each in Brazil and Spain.

The study was not initially intended to be a registrational study and was not planned with the expectation that it would be used to support seeking a new indication or a change in Priftin labeling. At the request of Sanofi, the CDC solicited financial disclosure forms from the study investigators and sub-investigators after the study was concluded. Only 105 forms out of 600 individuals named on the FDA 1572 form (approximately 18%) were returned; none of the returned forms reported financial interests. The returned financial disclosure forms are currently held by the CDC and were not released to Sanofi at the advice of legal counsel, but the CDC will release the forms directly to the FDA if asked. A letter from the CDC was included in the submission attesting to the above, and stating that Sanofi's role in Study 26 was limited to providing rifapentine for the trial free of charge.

Sanofi informed the FDA during the pre-NDA meeting that there would be no financial disclosure form submitted. Sanofi included an attestation that they were not involved in the planning or conduct of TBTC Study 26, that they are unaware of any particular financial arrangements between the CDC and TBTC Study 26 investigators, and that the investigators were not compensated by Sanofi for any activities related to the conduct of Study 26.

The CDC attests that the applicant was not involved in the design or conduct of the study and was not involved in the original data analysis. The applicant has adequately disclosed financial arrangement with the CDC and the study investigators and has pursued acceptable due diligence in obtaining financial arrangement records.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HALA H SHAMSUDDIN
10/24/2014

THOMAS D SMITH
10/24/2014