

## Supplementary Appendix

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

Supplement to: Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med* 2011;365:2155-66.

## Web Supplement

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## **Study Method Details**

### **Study exclusion criteria:**

Exclusion criteria were a) current confirmed tuberculosis, b) suspected tuberculosis, c) tuberculosis resistant to isoniazid or rifampin in the source case, d) history of treatment for >14 consecutive days with a rifamycin or >30 consecutive days with isoniazid during the previous 2 years, e) documented history of completing adequate treatment for active tuberculosis or latent *M. tuberculosis* infection in a HIV-seronegative person, f) history of sensitivity/intolerance to isoniazid or rifamycins, g) serum aspartate aminotransferase (AST) >5 times the upper limit of normal (ULN) if AST was determined, h) pregnant or lactating females, i) persons currently receiving or planning to receive HIV-1 therapy within 90 days after enrollment, or j) weight < 10.0 kg.

### **Statistical analysis details:**

Categorical variables were compared with the Pearson's chi-squared test and continuous variables with the Wilcoxon rank-sum test. Tuberculosis rates were determined per 100 p-y of follow-up and as a cumulative rate (percentage). The difference in the cumulative tuberculosis rate by study arm, and the 95% confidence interval of the difference, were determined. The proportion of adverse events among all persons who received  $\geq 1$  dose of study drug were compared by arm; for persons with > 1 event, only the first event was included. The average adverse event rate was also determined (number of events per 100 persons; included all adverse events). Univariate and multivariate risk factor analyses were performed to assess predictors of tuberculosis risk.

## **Dosing of Study Drugs**

### **3HP arm**

#### *Rifapentine:*

Persons weighing > 50.0 kg received rifapentine 900 mg once-weekly

Persons weighing  $\leq$  50.0 kg were dosed once-weekly according to the following scale:

<u>Weight</u>	<u>Dose</u>
10.0-14.0 kg	300 mg
14.1-25.0 kg	450 mg
25.1-32.0 kg	600 mg
32.1-50.0 kg	750 mg

#### *Isoniazid:*

Persons 2-11 years old received isoniazid 25 mg/kg (rounded up to the nearest 50 or 100 mg; 900 mg max) once-weekly

Persons  $\geq$  12 years old received isoniazid 15 mg/kg (rounded up to nearest 50 or 100 mg; 900 mg max) once-weekly

### **9H arm**

Persons 2-11 years old received isoniazid 10-15 mg/kg (round up to nearest 50 or 100 mg, 300 mg max) daily

Persons  $\geq$  12 years old received isoniazid 5 mg/kg (rounded up to nearest 50 or 100 mg; 300 mg max) daily

Pyridoxine (vitamin B6) 50 mg with each dose of isoniazid was recommended for participants in both study arms but not required.

## **Study Definitions**

Close contact with a tuberculosis case was defined as  $\geq 4$  hours (by participant self-report or in the estimation of the site investigator) in a shared airspace during a one-week period.

A broad definition of possible drug hypersensitivity was used: a) hypotension, urticaria, angioedema, acute bronchospasm, or conjunctivitis that occurred in relation to study drug; or b)  $\geq 4$  of the following (one of which had to be  $\geq$  grade 2) that occurred in relation to study drug: weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing, or chills.

## **Justification of the Non-inferiority Margin**

The judgment of the protocol team was that an absolute non-inferiority margin of 0.75% was clinically appropriate, given an expected event rate in the 9H arm of 1.5%. The relative non-inferiority margin of 50% was felt to be appropriate because the absolute expected event rate (1.5%) was low.

The non-inferiority margin also was appropriate statistically, and consistent with guidelines of the U.S. Food and Drug Administration (FDA).(1) The key aspect was to ensure that the event rate in the experimental arm (3HP) was better than placebo, under many possible scenarios. A sensitivity analysis was performed as described below.

The first step was to assume the largest acceptable margin (noted here as M1), which is defined as the effect of the active control (9H) over placebo (no-treatment), based on historical studies.

In this study, 9H was assumed to be 70% effective and the tuberculosis event rate without treatment was assumed to be 5%. Both assumptions were the best estimates available at the time the trial started in 2001. Therefore, the expected tuberculosis rate in the 9H arm was  $(1.0 - 0.7) \times 5\% = 1.5\%$ . M1 is the improvement that the 9H arm would make over no treatment:  $5\% - 1.5\% = 3.5\%$ .

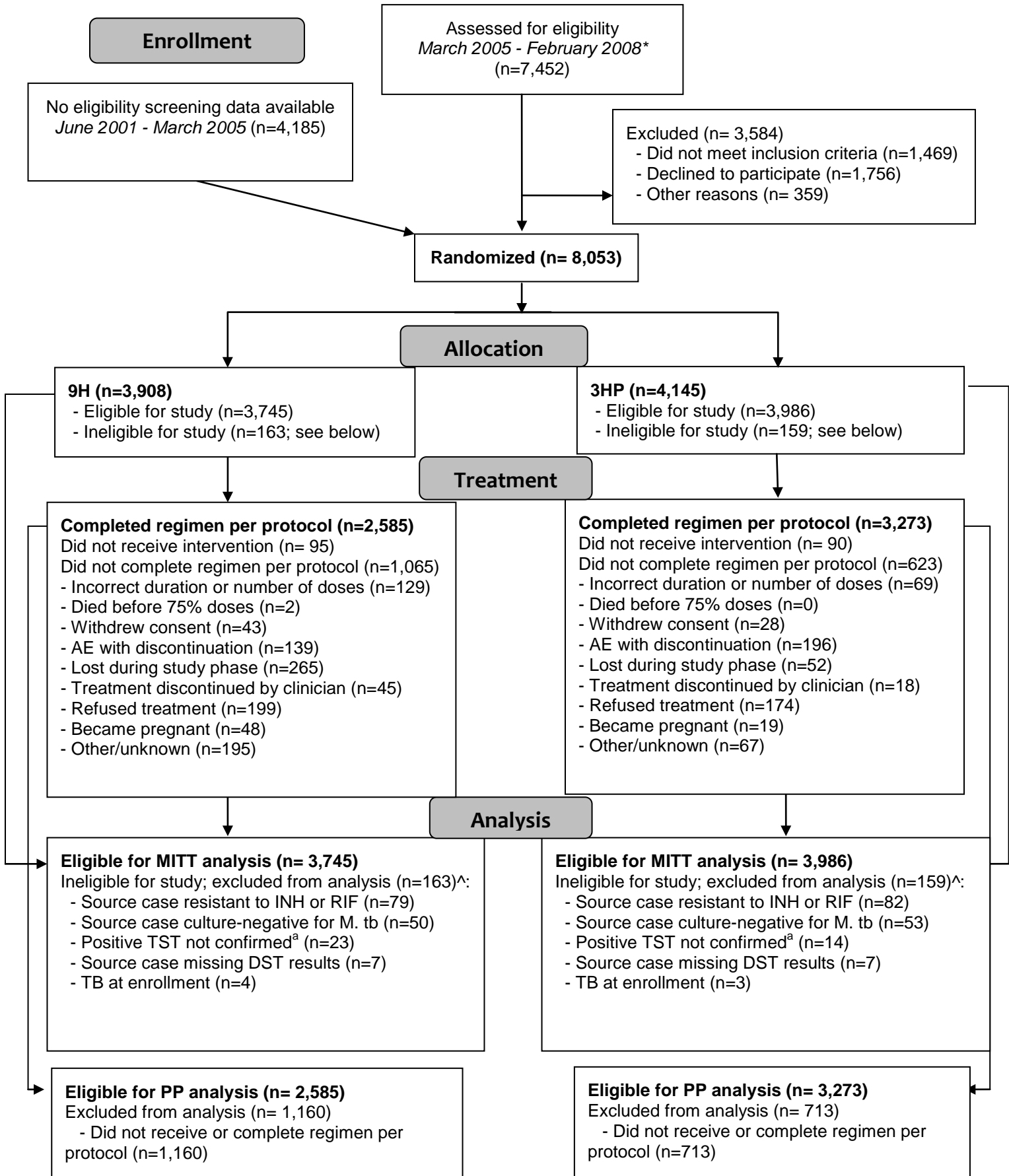
The second step was to select a non-inferiority margin (M2) that was not only clinically meaningful, but also preserved a large proportion of M1. A non-inferiority margin of 0.75% means that the tuberculosis rate in the 3HP arm could be 2.25% ( $1.5\% + 0.75\%$ ) and still be able to claim non-inferiority. In that scenario, the improvement that 3HP would make over no treatment would be  $5\% - 2.25\% = 2.75\%$ . This preserves 79% of M1, since  $2.75 / 3.5 = 0.79$ .

This was also determined from the following equation:  $1 - (0.75 / 3.5) = 0.79$

Large values of “preservation” are preferred. A value of 79% provides confidence that M1 was preserved. Therefore, the non-inferiority margin of 0.75% preserves 79% of M1.

We then conducted a sensitivity analysis, varying the effectiveness of 9H from 60% to 90% and the tuberculosis rate without treatment from 2% to 5%. There was still substantial preservation of M1, using a non-inferiority margin (M2) of 0.75%.

**Repository Figure 1. Flow Diagram of Study Participants—CONSORT Criteria.**



\* Eligibility screening data were obtained after March 2005, with implementation of an eligibility screening log. This was implemented in response to CONSORT reporting criteria, which were updated after the study began.(2)

^ Enrollment of participants was allowed before tuberculosis culture and susceptibility data were available in the source case. Participants ineligible because the source case was culture-negative for *M. tuberculosis*, had *M. tuberculosis* resistant to INH or RIF, or did not have susceptibility testing performed, were identified after enrollment.

<sup>a</sup> Positive TST not confirmed on repeat testing.

Abbreviations:

9H: 9 months of self-administered daily isoniazid

3HP: 3 months of directly-observed once-weekly rifapentine and isoniazid

DST: drug susceptibility testing

AE: adverse event

MITT: modified intention to treat

PP: per protocol

INH: isoniazid

RIF: rifampin

M. tb: *M. tuberculosis*

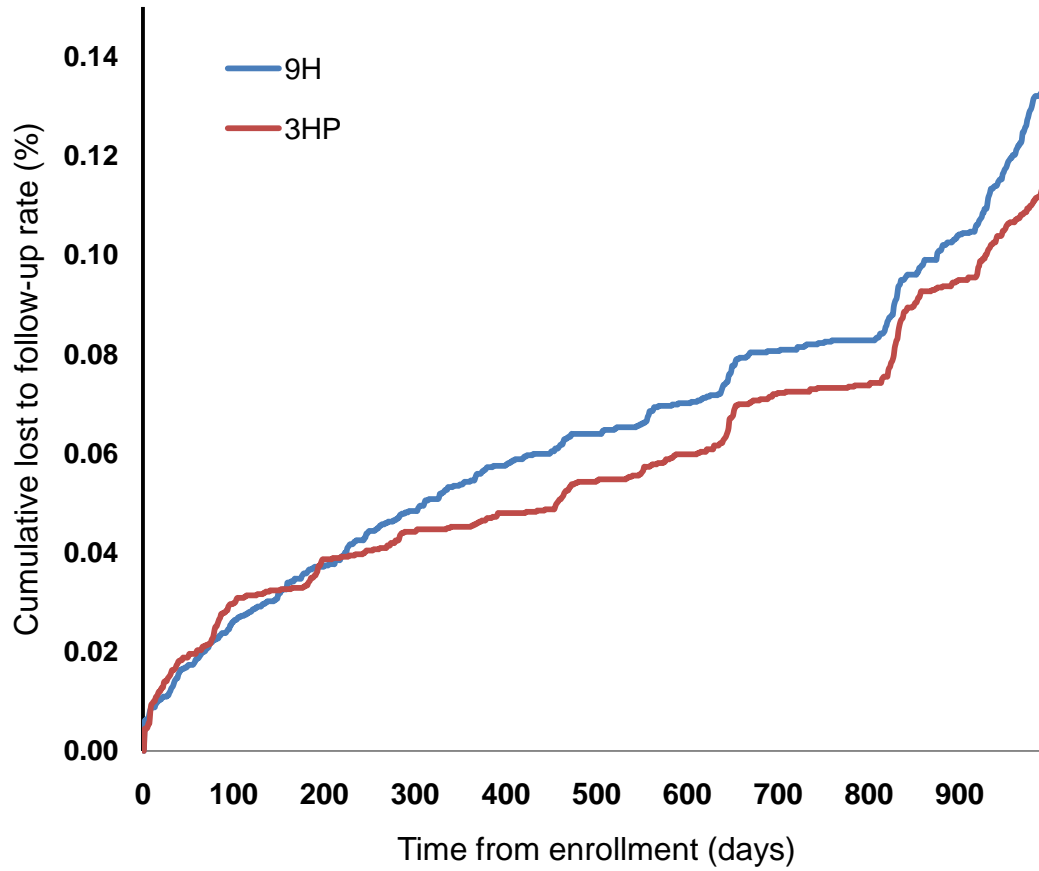
TST: tuberculin skin test

**Repository Table 1. Reasons for Study Ineligibility.** Among 8,053 participants randomized, 322 were ineligible for the study.

<b>Reason</b>	<b>N</b>	<b>% of Ineligible Participants</b>
Source TB case resistant to INH or RIF	161	50
Source TB case culture-negative for <i>M. tuberculosis</i>	103	32
Positive tuberculin skin test not confirmed	37	12
<i>M. tuberculosis</i> drug susceptibility test results not available for the source TB case	14	4
TB at enrollment	7	2
Total	322	100

Enrollment of participants was allowed before tuberculosis culture and susceptibility data were available in the source case. Participants ineligible because the source case was culture-negative for *M. tuberculosis*, had *M. tuberculosis* resistant to INH or RIF, or did not have susceptibility testing performed, were identified after enrollment.

**Repository Figure 2. Cumulative Lost to Follow-up Rate by Treatment Regimen.** Follow-up is from the time of enrollment. Log-rank P-value = 0.01.



**Repository Table 2. Number of Tuberculosis Cases and Event Rates by Study Arm.** Results of the modified intention to treat and per-protocol analyses 24 months after the last treatment dose. The difference in cumulative tuberculosis rate is the rate in the 3RPT/INH arm minus the rate in the 9INH arm. The non-inferiority margin is 0.75% for all analyses.

<b>Population</b>	<b>Study arm</b>	<b># of patients</b>	<b># TB cases</b>	<b>TB per 100 p-y</b>	<b>Cumulative TB rate (%)</b>	<b>Difference in cumulative TB rate</b>	<b>Upper bound of 95% confidence interval of the difference in cumulative TB rates (%)</b>
<b>MITT</b>	9H	3,651	12	0.18	0.37	-0.21	0.04
	3HP	3,914	6	0.08	0.16		
<b>Per Protocol</b>	9H	2,564	5	0.10	0.23	-0.10	0.14
	3HP	3,243	4	0.06	0.13		

TB: tuberculosis

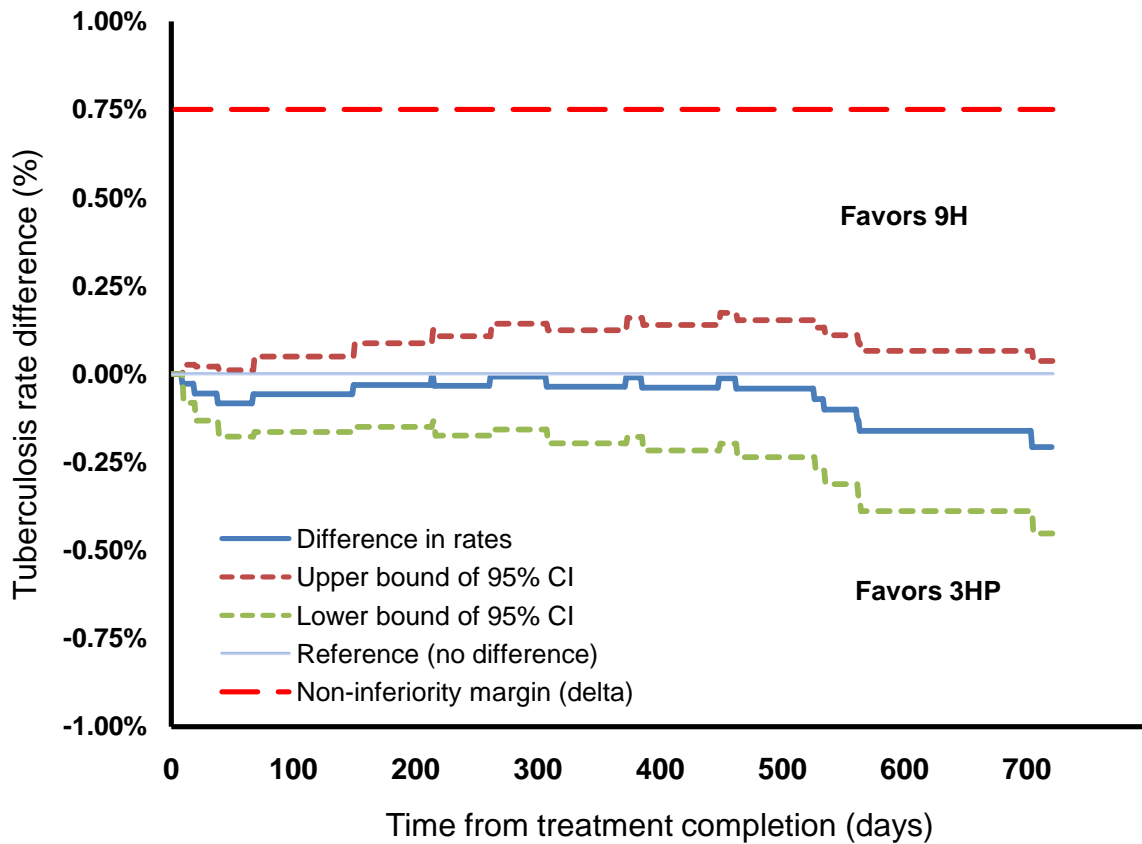
MITT: modified intention to treat

INH: isoniazid

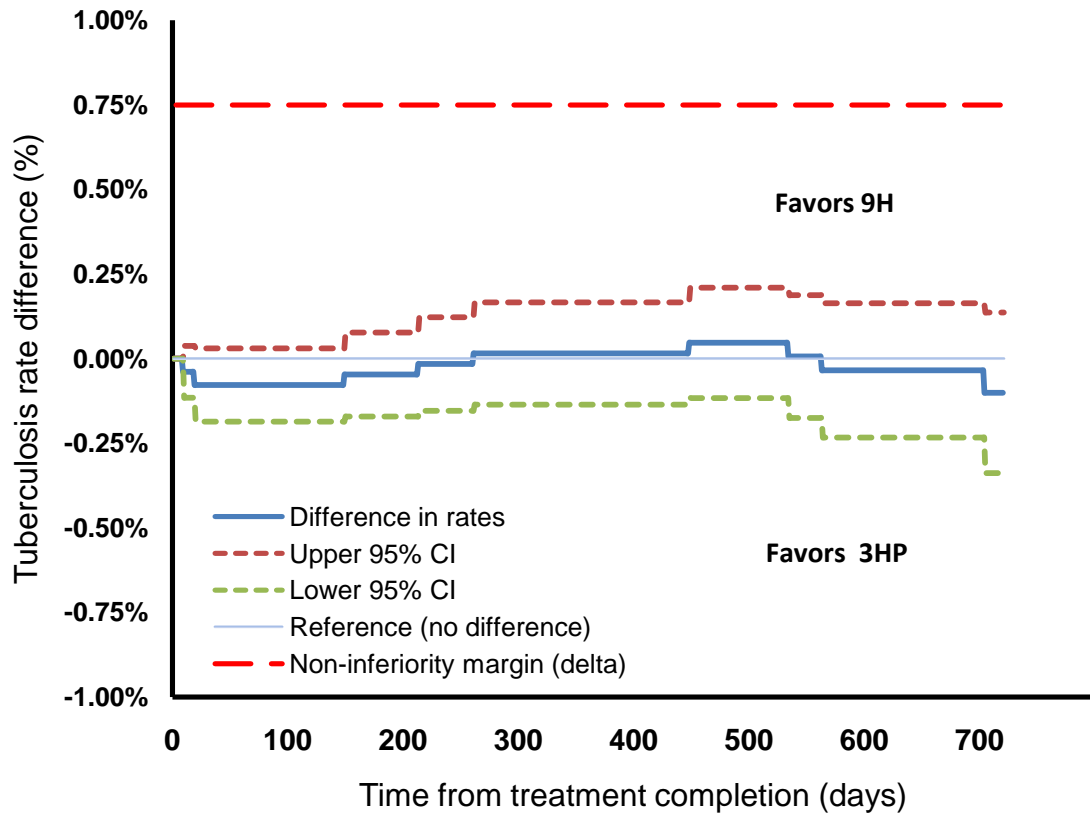
RPT: rifapentine

**Repository Figure 3. Difference in Tuberculosis Rates Between the Two Study Arms Over Time.** Modified intention-to-treat and per protocol study populations 24 months from the last treatment dose (2A and 2B). These analyses are for the primary endpoint of culture-confirmed tuberculosis in adults and culture-confirmed or culture-negative tuberculosis in children < 18 years old. The difference in event rates is the rate in the 3HP arm minus the rate in the 9H arm. The non-inferiority margin is 0.75%.

Repository Figure 3A. Modified intention-to-treat (24 months from last dose)

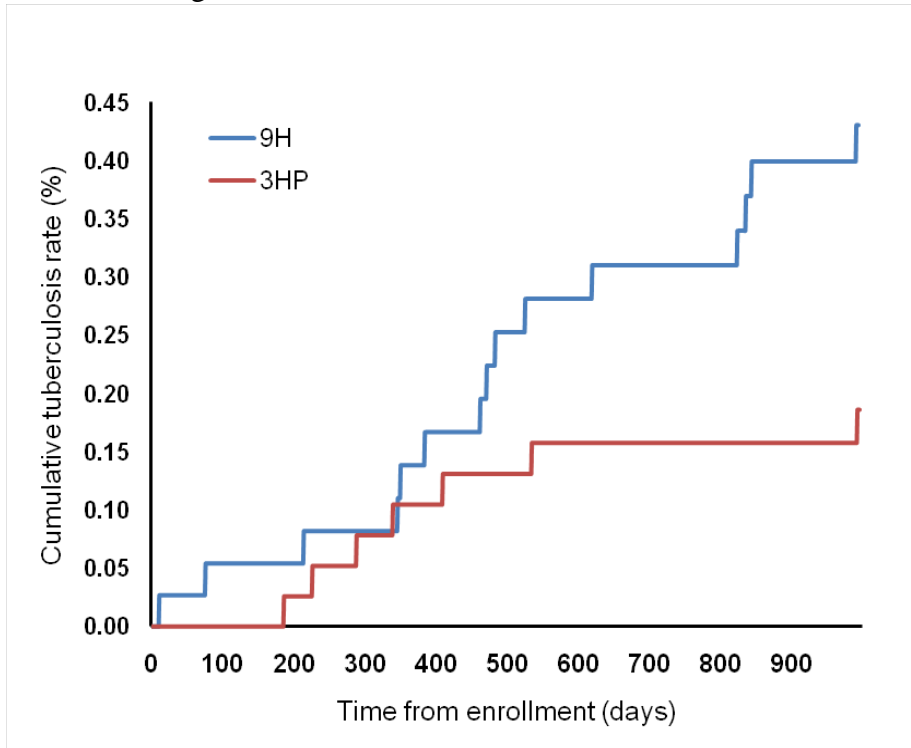


Repository Figure 3B. Per protocol (24 months from last dose)

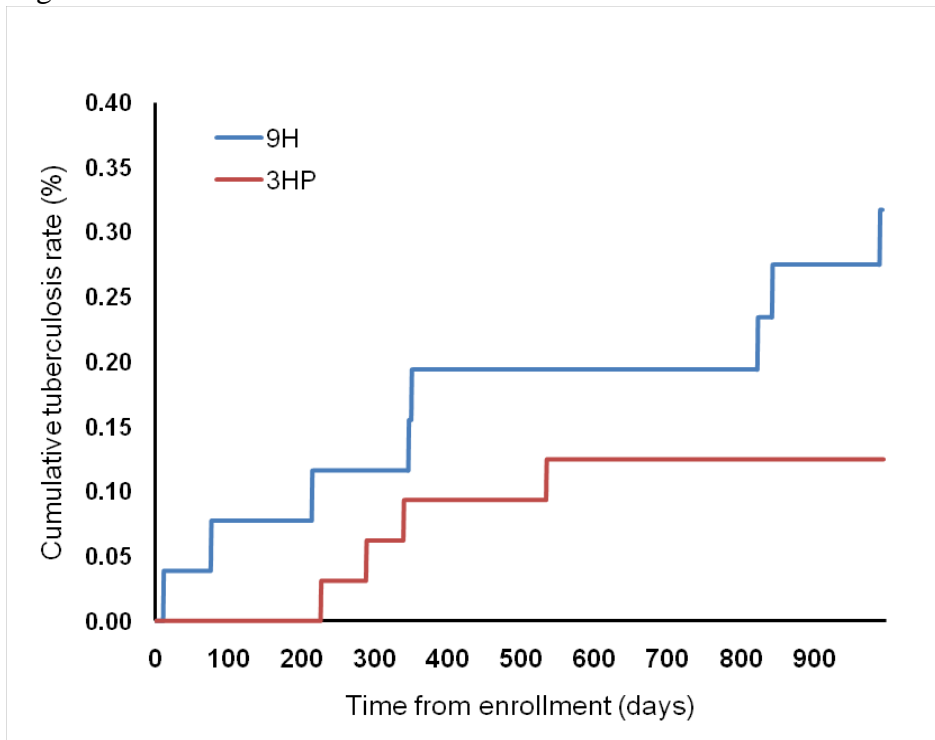


**Repository Figure 4. Cumulative Tuberculosis Event Rates by Treatment Regimen.**

Repository Figure 4.A. Modified intention to treat population followed up to 33 months from enrollment. Log-rank P-value = 0.06.

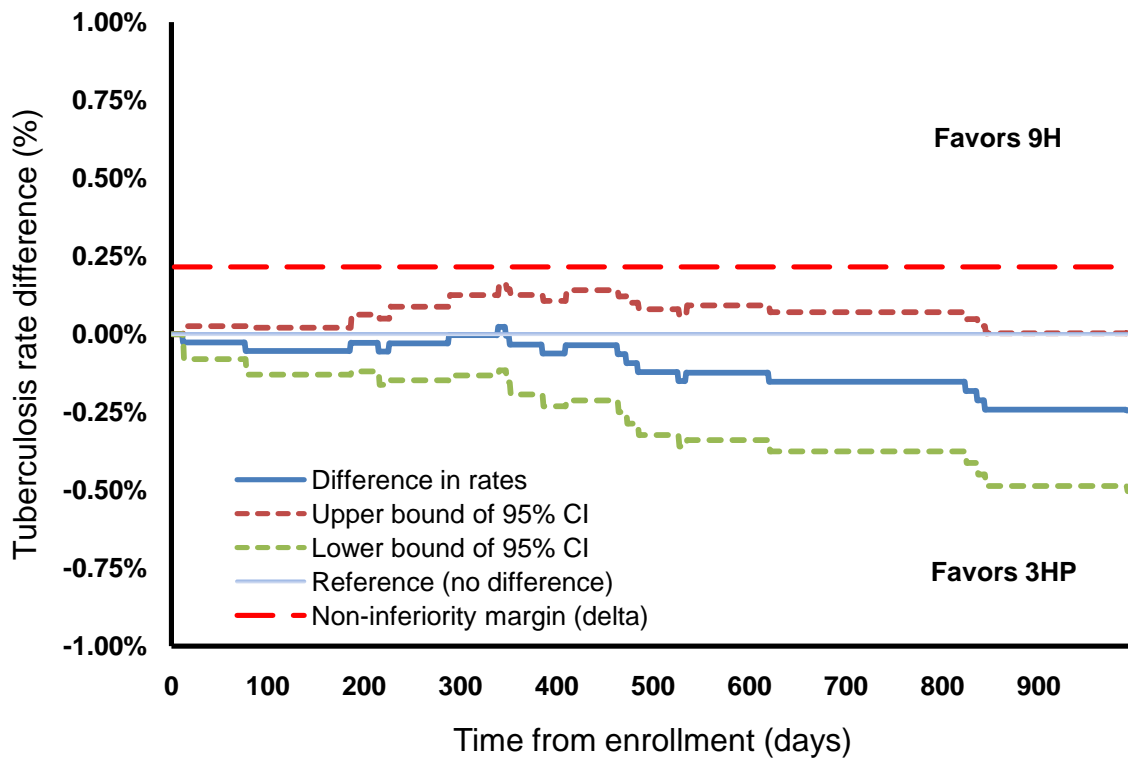


Repository Figure 4.B. Per protocol population followed 33 months from enrollment. Log-rank P-value = 0.12.

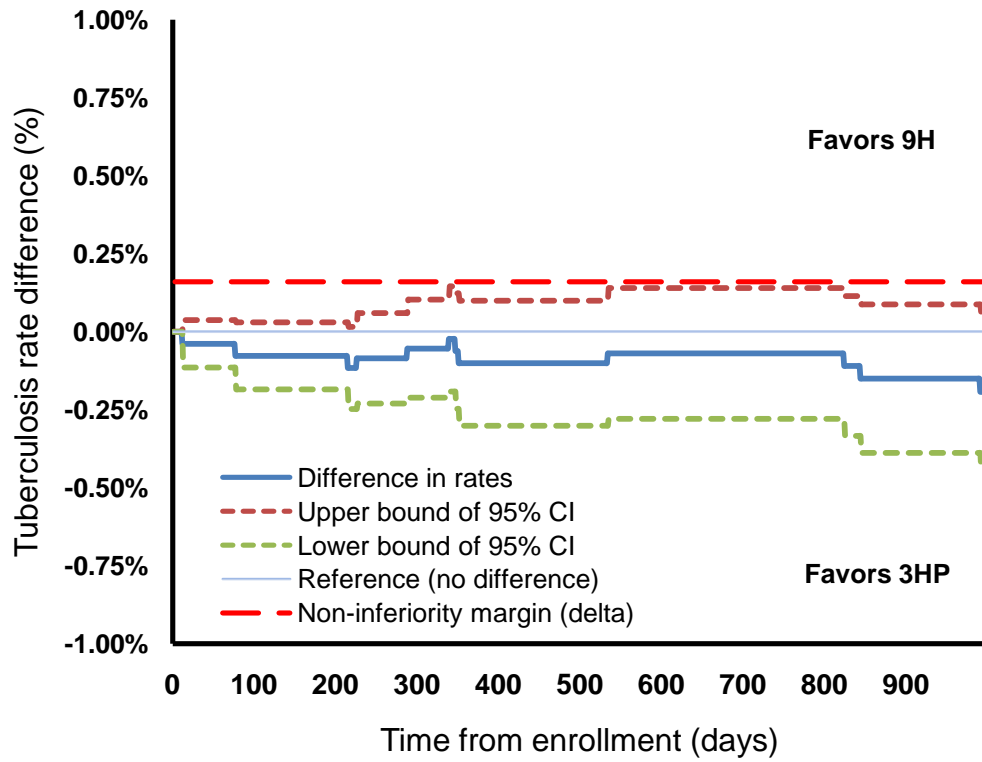


**Repository Figure 5. Difference in Tuberculosis Rates Between the Two Study Arms Over Time.** Modified intention-to-treat (MITT) and per protocol (PP) study populations up to 33 months from enrollment (Repository Figure 5A and 5B). These analyses are for the primary endpoint of culture-confirmed tuberculosis in adults and culture-confirmed or culture-negative tuberculosis in children < 18 years old. The difference in event rates is the rate in the 3HP arm minus the rate in the 9H arm. The non-inferiority margin is 0.22% for the MITT analysis and 0.16% for the PP analysis.

Repository Figure 5A. Modified intention-to-treat (33 months from enrollment)



Repository Figure 5B. Per protocol (33 months from enrollment)



**Repository Table 3. All Grade 3 and 4 Adverse Events by Treatment Regimen and System Organ Classification.** Adverse events were classified by the MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class (SOC). They are presented in the order of frequency of total number of events. The number of events in each SOC are provided.

<b>System Organ Class</b>	<b>9H</b> n=244	<b>3HP</b> n=229
<b>Hepatobiliary disorders</b>		
SAE*	4	3
Non-SAE	84	22
<b>Immune system disorders</b>		
SAE	1	8
Non-SAE	11	79
<b>Infections and infestations</b>		
SAE	13	5
Non-SAE	8	7
<b>Nervous system disorders</b>		
SAE	2	3
Non-SAE	11	16
<b>Injury, poisoning and procedural complications</b>		
SAE	11	3
Non-SAE	7	7
<b>Psychiatric disorders</b>		
SAE	10	2
Non-SAE	4	7
<b>Gastrointestinal disorders</b>		
SAE	10	5
Non-SAE	2	5
<b>General disorders and administration site conditions</b>		
SAE	4	3
Non-SAE	5	6
<b>Metabolism and nutrition disorders</b>		
SAE	1	0
Non-SAE	10	7
<b>Musculoskeletal and connective tissue disorders</b>		
SAE	2	3
Non-SAE	5	5

<b>Vascular disorders</b>		
SAE	3	0
Non-SAE	3	9
<b>Surgical and medical procedures</b>		
SAE	7	5
Non-SAE	2	0
<b>Respiratory, thoracic and mediastinal disorders</b>		
SAE	1	2
Non-SAE	4	2
<b>Cardiac disorders</b>		
SAE	2	5
Non-SAE	0	2
<b>Neoplasms benign, malignant and unspecified</b>		
SAE	3	1
Non-SAE	2	1
<b>Blood and lymphatic system disorders</b>		
SAE	1	1
Non-SAE	2	1
<b>Renal and urinary disorders</b>		
SAE	0	0
Non-SAE	3	2
<b>Skin and subcutaneous tissue disorders</b>		
SAE	0	1
Non-SAE	2	0
<b>Ear and labyrinth disorders</b>		
SAE	0	0
Non-SAE	1	0
<b>Eye disorders</b>		
SAE	0	0
Non-SAE	1	0
<b>Reproductive system and breast disorders</b>		
SAE	0	0
Non-SAE	0	1

\*Severe Adverse Event

**Repository Table 4. All Deaths by Treatment Regimen and ICD-9 Code.**

<b>ICD9 Category</b>	<b>9H n=39</b>	<b>3HP n=31</b>
Malignant neoplasms (cancer)*	15	8
Intentional injuries	6	1
Diseases of heart*	4	8
Unintentional injuries*	3	3
Chronic liver disease or cirrhosis*	2	4
Hypertension (with or w/o renal disease)	2	1
AIDS	1	1
Cerebrovascular diseases*	1	4
Chronic lower respiratory diseases*	1	0
Chronic pancreatitis	1	0
Diabetes mellitus	1	0
Septicemia	1	1
Unknown	1	0

\*The 11 deaths that occurred on therapy or within 60 days of last dose are included among these categories.

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