Efficacy and safety of high-dose rifampin in pulmonary tuberculosis: a randomized controlled trial

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At a Glance Commentary:

Scientific Knowledge on the Subject

The standard of care for patients with new pulmonary tuberculosis is a six-month, four-drug regimen that includes rifampin for the full course of therapy. Attempts to further shorten tuberculosis therapy in the 1970s with higher, intermittent doses of rifampin were unsuccessful due to an apparent increase in toxicity. Renewed interest in tuberculosis treatment shortening developed earlier this century, with trials of fluoroquinolones, rifapentine, and a shortened regimen in patients at lower risk for poor outcomes. We sought to systematically examine the concept that increased daily doses of rifampin could shorten standard therapy for tuberculosis and improve treatment outcomes without increased toxicity.

What This Study Adds to the Field

This blinded, randomized, controlled Phase II clinical trial assessed differences across three daily oral doses of rifampin (10, 15, and 20 mg/kg) in change in elimination rate of *Mycobacterium tuberculosis* in sputum and frequency of rifampin-related adverse events. We found that doses of 15 and 20 mg/kg/day resulted in more rapid change in counts of *M. tuberculosis* and a similar frequency of rifampin-related adverse events. This is the first controlled study to show both dose-and exposure-response of rifampin on sputum sterilization. Our findings support the continued investigation of higher doses of rifampin, beyond 20 mg/kg, for potential treatment shortening.

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Abstract

Rationale: We examined whether increased rifampin doses could shorten standard therapy for tuberculosis without increased toxicity.

Objectives: To assess the differences across three daily oral doses of rifampin in change in elimination rate of *Mycobacterium tuberculosis* in sputum and frequency of rifampin-related adverse events.

Methods: We conducted a blinded, randomized, controlled Phase II clinical trial of 180 adults with new smear-positive pulmonary tuberculosis, susceptible to isoniazid and rifampin. We randomized 1:1:1 to 10, 15, and 20 mg/kg/day of rifampin during the intensive phase. We report the primary efficacy and safety endpoints: change in elimination rate of *M. tuberculosis* $\log_{10}$ colony forming units and frequency of grade 2 or higher rifampin-related adverse events. We report efficacy by treatment arm and by primary (AUC/MIC) and secondary (AUC) pharmacokinetic exposure.

Measurements and Main Results: Each 5 mg/kg/day increase in rifampin dose resulted in differences of -0.011 (95%CI, -0.025 – +0.002;*P*=0.230) and -0.022 (95%CI, -0.046 – -0.002;*P*=0.022) $\log_{10}$ colony forming units/mL/day in the modified intention-to-treat and per-protocol analyses, respectively. Elimination rate in the per-protocol population increased significantly with rifampin $AUC_{0\text{-}6}$ (*P*=0.011) but not with $AUC_{0\text{-}6}/MIC_{99.9}$ (*P*=0.053). Grade 2 or higher rifampin-related adverse events occurred with similar frequency across the three treatment arms: 26(43.3%), 31(51.7%), and 23(38.3%) participants had at least one event (*P*=0.7092) up to 4 weeks after the intensive phase. Treatment failed or disease recurred in 11(6.1%) participants.

Conclusions: Our findings of more rapid sputum sterilization and similar toxicity with higher rifampin doses support investigation of increased rifampin doses to shorten tuberculosis treatment.

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Keywords: tuberculosis, rifampin, randomized controlled trial, treatment efficacy, adverse drug event

Introduction

Tuberculosis is the leading infectious cause of death worldwide, killing 1.7 million in 2016 (1). Standard treatment for the annual estimated 10.4 million patients with new pulmonary tuberculosis is a six-month, four-drug regimen including rifampin throughout (2).

Combining rifampin and pyrazinamide in the early 1970s shortened tuberculosis treatment from 18 to 6 months (3). Further attempts to shorten tuberculosis therapy in the 1970s were guided by perceived cost constraints: any increase of the dose was matched by decreased frequency of administration. The resulting higher, intermittent doses of rifampin led to increased toxicity (4-6). Ultimately, the 600 mg daily dose of rifampin was selected as the standard (7). Renewed interest in tuberculosis treatment shortening developed over the last 20 years, with preclinical and clinical studies of fluoroquinolones and one trial of a further-shortened regimen in patients with noncavitary disease and rapid bacteriological response (8-14). Prior to the initiation of the present study, a Phase II trial of treatment shortening with another rifamycin, rifapentine, was published; further work on treatment shortening with rifapentine was subsequently pursued (15-17).

Daily dose optimization of rifampin remained a priority. Unlike moxifloxacin and rifapentine, rifampin is an established first-line drug, available throughout the world, from multiple suppliers, now for pennies a capsule. It is also available in combination formulations. Of the four current first-line agents, rifampin has the most potent sterilizing activity and has been established as key to the continuation phase of treatment (18, 19). At the 600 mg daily dose, rifampin is well-

tolerated (20-23). However, concern about the toxicity of rifampin at higher doses persists pursuant to trials of intermittent dosing (6, 20, 24).

While multiple controlled trials began to evaluate higher rifampin doses in African populations (25-27), and a single observational study evaluated rifampin concentrations in routine conditions in Peru (28), none evaluated, under controlled conditions, the concentration of rifampin and its concentration-dependent activity in Latin American patients. Prior evidence indicates important population variability in these measures for antituberculous drugs (29-32). No other late-stage clinical study has explored efficacy as a function of the pharmacokinetic/pharmacodynamic parameter thought to best predict rifampin efficacy (AUC/MIC) (22, 33-35). The present clinical trial entitled “Evaluation of high-dose rifampin in patients with new, smear-positive tuberculosis” (HIRIF) was designed to examine the concept that increased rifampin doses could shorten standard therapy for tuberculosis and improve treatment outcomes without increased toxicity. The primary objectives of this study were to assess the differences across three daily oral doses of rifampin (10, 15, and 20 mg/kg) in: plasma concentrations of rifampin; change in elimination rate of *Mycobacterium tuberculosis* in sputum; and frequency of grade 2 or higher adverse events (AEs) related to rifampin. Here we report the primary efficacy and safety endpoints. The pharmacokinetic results have been previously published (36), and some of the results of this study have been previously reported in the form of abstracts (37-39).

Methods

Design

HIRIF was a blinded, randomized, controlled Phase II clinical trial registered under an investigational new drug application with the U.S. Food and Drug Administration (106635) and with ClinicalTrials.gov (NCT01408914) investigating the pharmacokinetics, efficacy, and safety of higher doses of rifampin in patients with pulmonary tuberculosis. Participants were identified and referred for enrollment from health centers in Lima, Peru between September 2013 and February 2015. Eligible participants were previously untreated adults (18-60 years old) with smear-positive disease (≥2+) and strains susceptible to isoniazid and rifampin. Exclusion criteria included a contraindication to rifampin and certain extrapulmonary manifestations of tuberculosis. All participants provided written informed consent. Additional details on study methods are provided in the published protocol (40) and online supplement.

Intervention

Participants were randomly allocated (1:1:1) in blocks of varying size to receive 10, 15, or 20 mg/kg/day of rifampin during the 8-week intensive phase (see Table E1 for dosing by weight band). The randomization sequence was generated by the unblinded study statistician and programmed into the electronic data capture (EDC) system. All other study staff (including laboratory staff) were blinded, except pharmacy staff who received the arm assignment from the EDC and prepared study-drug kits. Standard doses of rifampin and companion drugs (isoniazid, pyrazinamide, ethambutol) were delivered through fixed-dose combinations (FDCs) supplied by MacLeods Pharmaceuticals (Mumbai, India) (2). These were supplemented by 150 mg capsules of rifampin and matched placebo donated by Sanofi (Paris, France). During the 18-week

continuation phase, participants received isoniazid supplied by Micro Labs Limited (Bangalore, India) and rifampin, both dosed at 10 mg/kg thrice weekly. Participants received pyridoxine 50 mg thrice weekly throughout treatment. Treatment was ambulatory and directly observed.

Protocol-defined safety halts occurred when rifampin-related serious AEs met prespecified halting criteria (Table E2) (40). During safety halts, all subjects were treated with a standard regimen according to local guidelines (with an intensive phase rifampin dose of 10 mg/kg/day). When the sponsor and the data safety and monitoring board determined that the study could resume, participants in the intensive phase of treatment reinitiated their assigned experimental doses.

Outcomes

The primary pharmacokinetic/pharmacodynamic (PK/PD) endpoint, area under the concentration-time curve (AUC) of rifampin in plasma at steady state divided by the minimum inhibitory concentration of 99.9% of *M. tuberculosis* ($MIC_{99.9}$), has been previously reported (36). The primary efficacy endpoint was the change in elimination rate of *M. tuberculosis* $\log_{10}$ colony forming units (CFU) per mL in overnight pooled sputum samples collected throughout the intensive phase and cultured on 7H11 Middlebrook medium. Secondary efficacy endpoints included proportion of culture conversion in Löwenstein-Jensen (LJ) medium at 8 weeks, and proportion of unfavorable outcomes (treatment failure, recurrence after cure, or death) at 12 months. We classified recurrent disease with identical 24-locus mycobacterial interspersed repetitive units–variable number tandem repeat (MIRU-VNTR) sequencing as relapsed disease, and nonidentical MIRU-VNTR as reinfection. The primary safety endpoint was the frequency of

grade 2 or higher rifampin-related AEs, per the Division of Microbiology and Infectious Diseases' Adult Toxicity Table (41), during the intensive phase and up to 4 weeks thereafter.

Statistical Analysis

We defined the intention-to-treat (ITT) population as all participants who received at least one dose of study medication. The modified intention-to-treat (mITT) population (prespecified as primary for efficacy) included those in the ITT population with more than one non-missing, detectable, and plausible quantitative culture result. The per-protocol (PP) population included those in the mITT population whose experimental rifampin dose was not affected by study halts. Sensitivity analyses were performed on all participants with at least one $\log_{10}$CFU/mL count. We analyzed $\log_{10}$CFU/mL using linear and nonlinear mixed effects models in NONMEM 7.2 (ICON plc, Dublin, Ireland), Perl-speaks-NONMEM 4.4.0 (Uppsala University, Uppsala, Sweden) and R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Monophasic and biphasic structural models were fitted, by treatment arm and pharmacokinetic exposure, using the M3 partial likelihood method and Laplacian estimation with interaction.

We used the one-sided Cochran-Armitage test for trend with 5% significance to compare proportions of participants who experienced at least one grade 2 or higher rifampin-related AE. We used the log-rank test to compare the time to AEs. We performed similar tests for secondary analyses of rifampin-related hepatic AEs and serious AEs (SAEs). A sensitivity analysis excluded AEs that occurred during study halts in the 15 and 20 mg/kg arms. We performed all safety analyses in Stata/SE 14.2 (StataCorp LLC, College Station, TX).

Results

We screened 351 patients for eligibility; of these, 180 were randomized to receive study drug, 60 to each arm (Figure 1). Three study halts occurred during the study. The data safety and monitoring board recommended restarting enrollment and study dosing after each of the halts. Details on the study halts are provided in Table E2. The trial ended when all enrolled participants completed follow-up.

The mITT dose-efficacy analysis included 174 participants. Six participants were excluded for inadequate data: four had only one CFU observation; one had all CFU observations below the limit of detection (<10 CFU/mL); and one had implausibly discrepant CFUs in two samples obtained 9 days apart. The PP dose-efficacy analysis included 132 patients in the mITT population whose intensive phase rifampin dosing was unaffected by study halts. The mITT and PP exposure-efficacy analyses included 163 and 126 patients from the respective dose-efficacy populations who completed a PK sampling visit (Figure 1). All 180 participants were included in the safety analysis. Most participants were young (median age 25) and male (63.3%). Median weight was slightly higher in the 15 mg/kg arm, 55.4 kg (interquartile range [IQR], 49.2-60.5 kg) compared to 53.5 kg (IQR, 50.6-59.6 kg) and 54.9 kg (IQR, 50.3-61.7 kg) in the 10 and 20 mg/kg arms, respectively. Over half of participants had a baseline smear grade of 3+ (51.7%); slightly more patients in the 15 mg/kg arm (60.0%) than in the 10 mg/kg (46.7%) and in the 20 mg/kg (48.3%) arms had a 3+ smear grade. The mean baseline mycobacterial load was 5.2 $\log_{10}$CFU/mL. The mean baseline loads were 4.8 and 5.5 $\log_{10}$CFU/mL among participants with 2+ and 3+ smear grades, respectively. Cavitary disease was present in 66 (37.1%). HIV coinfection and diabetes were rare, present in 5 (2.8%) and 1 (0.6%) participants respectively.

Other than weight and smear grade, the distribution of sociodemographic characteristics, comorbidities, clinical indicators of disease severity, and mycobacterial load were similar across arms. Participants received median rifampin doses of 450 mg (IQR, 450-600 mg), 900 mg (IQR, 600-900 mg), and 975 mg (IQR, 750-1200 mg) in the 10, 15, and 20 mg/kg arms, respectively (Table 1).

Efficacy

Efficacy outcomes are shown in Tables 2 and 3, and Figure 2. A monophasic model of bacterial elimination best described the data. We estimated the difference in elimination rate between the treatment arms as -0.011 (95% confidence interval [CI], -0.025 – 0.002) $\log_{10}$CFU/mL/day for each 5 mg/kg increase in rifampin dose in the mITT population (*P*=0.230). In the PP population, the difference was -0.022 (95% CI, -0.046 – -0.002; *P*=0.022). Elimination rate in the mITT population did not increase with plasma rifampin $AUC_{0\text{-}6}$ (-0.001 $\log_{10}$CFU/mL/day per 1 log increase in $AUC_{0\text{-}6}$; 95% CI, -0.003 – 0.001; *P*=0.750) or $AUC_{0\text{-}6}/MIC_{99.9}$ (-0.002 $\log_{10}$CFU/mL/day per 1 log increase in $AUC_{0\text{-}6}/MIC_{99.9}$; 95% CI, -0.005 – 0.002; *P*=0.330). Elimination rate in the PP population increased with plasma rifampin $AUC_{0\text{-}6}$ (-0.017 $\log_{10}$CFU/mL/day per 1 log increase in $AUC_{0\text{-}6}$; 95% CI, -0.029 – -0.007; *P*=0.011), but not with $AUC_{0\text{-}6}/MIC_{99.9}$ (-0.010 $\log_{10}$CFU/mL/day per 1 log increase in $AUC_{0\text{-}6}/MIC_{99.9}$; 95% CI, -0.021 – 0.000; *P*=0.053). These results were not affected by adjustment for important baseline covariates including age, sex, and extent of radiological disease. The proportion of participants with 8-week culture conversion in LJ medium was nearly identical across the three treatment arms (76.7%, 73.3%, and 75.0%, respectively). Eleven (6.1%) participants experienced unfavorable outcomes by the end of the 12-month follow-up (7.5% of the 147 participants in

whom 12-month status could be assessed). Five (2.8%) participants experienced treatment failure. Of these, three (60%) were in the 10 mg/kg arm. Six (3.3%) more experienced recurrent disease, three (50%) in the 10 mg/kg arm; two (33%) were confirmed relapses by MIRU-VNTR sequencing. There were no deaths during the study. A detailed description of all treatment failure and recurrence outcomes is provided in Table E3.

Safety

The frequency of grade 2 or higher rifampin-related AEs was similar across treatment arms: 26 (43.3%), 31 (51.7%), and 23 (38.3%) of participants in the 10, 15, and 20 mg/kg arms respectively had at least one event (P=0.7092) (Tables 4 and E4). Time to first grade 2 or higher rifampin-related AE was also similar across arms (P=0.3610; Figure E1). The frequency and time to grade 2 or higher rifampin-related *hepatic* AEs and the frequency of SAEs were similar across arms (Tables 4-5). Results were similar when we excluded AEs that occurred during study halts in the experimental arms (Table E5).

The distribution of participants with at least one AE stratified by organ system is shown in Table E6. The most common AEs were hepatic (24.4%), gastrointestinal (14.4%), musculoskeletal (12.2%), and respiratory (11.7%). Nine SAEs occurred in eight participants during the entire study. Of these, six SAEs occurred in five participants during the safety period; four were rifampin-related (Table 5). A detailed description of all SAEs is provided in Table E7.

Discussion

The present study is the first clinical trial to show dose- and exposure-response of higher doses of rifampin under conditions of combination therapy. Higher rifampin doses and exposure resulted in an increase in the rate of sputum culture sterilization. These findings build on pharmacokinetic results from the present study and others showing that rifampin exposure increases at least proportionally with higher doses (25, 36), by clearly demonstrating that elimination rate is also related to rifampin $AUC_{0\text{-}6}$. These dose- and exposure-related efficacy findings are consistent with the results of the PanACEA MAMS-TB-01 trial (NCT01785186). This latter study found that rifampin doses of 20 mg/kg are unlikely to permit treatment shortening and that the optimal dose of rifampin is likely higher than 20 mg/kg (26). The statistically nonsignificant increase in culture negativity in the 20 mg/kg arm of the RIFATOX trial (ISRCTN55670677) also suggests that this dose may not be sufficient for treatment shortening (42).

The present study characterized the consistent impact of both rifampin dose and exposure on efficacy. Other analyses were not statistically significant: the analysis of 8-week culture conversion in LJ medium, the mITT analysis of dose and exposure as measured by $AUC_{0\text{-}6}$ and $AUC_{0\text{-}6}/MIC_{99.9}$ on the primary endpoint of change in $log_{10}CFU/mL$, and the PP analysis of exposure as measured by $AUC_{0\text{-}6}/MIC_{99.9}$. There are several potential explanations for these findings. First, the study was not powered for the 8-week binary, relatively insensitive, secondary endpoint. Second, the mITT efficacy estimates were affected by protocol-defined study halts. The use of standard rifampin dosing among all participants during study halts may have diminished the effect of the higher doses, biasing the effect estimate of dose towards the

null. This explanation is supported by the significant effect of dose detected in the PP analysis, which includes only the 132 (73.3%) participants who received their assigned rifampin dose for the full intensive phase. Study halts may have also biased the effect of exposure towards the null in the mITT population. Since rifampin exposure was not measured during study halts, the estimates of rifampin exposure in experimental arm participants who received standard rifampin dosing during study halts likely overestimate overall rifampin exposure. Given the effect of study halts on both dose- and exposure-response estimates in the mITT population, we feel that the PP population is less biased than the mITT population for the efficacy analysis, even though the PP population was the prespecified secondary analysis population.

Third, 1:1:1 randomization yielded median rifampin doses of 450, 900, and 975 mg in the 10, 15, and 20 mg/kg arms, respectively. Since median weights for all three arms fell in the 53-55 kg range, we expected that median rifampin doses would approach 600, 900, and 1200 mg, the assigned rifampin doses for the 55-70 kg weight band. However, more than half of study participants in the 10 mg/kg arm were in the two lowest rifampin weight bands, more than half in the 15 mg/kg arm were in the two highest weight bands, and the 20 mg/kg arm had the same number of participants in the two lowest and two highest weight bands. Consequently, the median difference in dose between the 15 mg/kg and 20 mg/kg arms was only 75 mg. These subtle differences in assigned rifampin doses (and consequent exposures) could have biased our results, reducing the apparent activity of the 20 mg/kg arm and the ability to distinguish a dose-response effect.

The effect of rifampin $AUC_{0-6}/MIC_{99.9}$ (the primary PK/PD endpoint) on sputum culture sterilization was of only borderline statistical significance. Prior preclinical studies have suggested that rifampin AUC/MIC is a strong predictor of concentration-dependent killing (22, 33). Clinical studies of patients receiving combination therapy have shown mixed results. Others have shown that rifampin AUC alone is an important predictor of clinical outcomes (32), and that its predictive ability may be bolstered by MIC information (34). However, a more recent study found no relationship between rifampin AUC/MIC and 2-month culture conversion (35). The distribution of susceptible rifampin MICs in our sample was higher than in the latter study (35), albeit within previously published ranges (34, 43). We did not find that rifampin MICs varied across levels of AUC to suggest that the effect of rifampin $AUC_{0-6}/MIC_{99.9}$ was attenuated by selection bias. Our findings suggest that rifampin $AUC_{0-6}/MIC_{99.9}$ was not as strong of a predictor of sputum sterilization as rifampin AUC_{0-6}, and that there may be a role for higher doses of rifampin in populations with susceptible rifampin MICs on the higher end of the distribution. In addition, the present analysis of rifampin $MIC_{99.9}$ does not capture the activity of rifampin metabolites which may contribute to treatment efficacy.

Despite our inclusion criterion of baseline sputum smear grade of 2+ or higher, we found a mean baseline mycobacterial load of 5.2 $\log_{10}$CFU/mL, approximately tenfold lower than in previous studies (8, 44). Low baseline loads have been reported in other settings, such as Hong Kong, Tanzania, and South Africa (25, 27, 45, 46). In the present study, low baseline loads may have contributed to the selection of a monophasic model of elimination by rifampin dose. This is distinct from the biphasic model selected to best represent the data in a study of fluoroquinolone-containing regimens (8). Our findings are consistent with those of a 14-day early bactericidal

activity study by the TB Alliance, which did not show a pronounced initial fall in the mycobacterial load among patients receiving standard therapy who had a mean baseline load of 5.399 $\log_{10}$CFU/mL (47), and by a recent observation that the 0-2 day early bactericidal activity of isoniazid-based treatments is strongly correlated with pretreatment mycobacterial load (46).

We found no difference in the secondary efficacy outcomes of 8-week culture conversion or in the frequency of treatment failure and disease recurrence across arms. The frequencies of treatment failure and recurrence we observed are comparable to those of standard therapy in other clinical trials (16, 19, 48). However, these relatively rare events occurred disproportionately in the 10 mg/kg arm, in which the median rifampin dose was 450 mg daily. We previously reported that 81% of the patients in the 20 mg/kg arm and only 33% of those of in the 10 mg/kg arm achieved a C_{max} of >8 mg/L, the low end of the targeted range (36). Others have reported that standard rifampin dosing through FDCs has resulted in suboptimal C_{max} <8 mg/L (35). Taken together, these findings suggest that standard doses of rifampin at 10 mg/kg may have compromised treatment efficacy and that the 20 mg/kg dose should be considered for dosing to maximize efficacy pending results of studies evaluating even higher doses. This has important implications for the use of FDCs, which are currently recommended over separate drug formulations in the treatment of drug-susceptible tuberculosis (49). Current guidelines recommend maximum rifampin doses of 600 mg daily (2), or 750 mg daily when using FDCs containing 150 mg of rifampin each (50). Under programmatic settings, supplementation with loose rifampin would be required to achieve higher doses.

We did not observe an increased risk of toxicity with rifampin doses up to 20 mg/kg delivered over 8 weeks. We found similar results when we excluded adverse events that occurred during study halts in the experimental arms. Our power calculation assumed a 10% frequency of grade 2 or higher rifampin-related AEs in the control arm. With 43.3% of control arm participants having at least one event, there was increased power over what was anticipated: we had more than 80% power to rule out a toxicity difference of 20% between the control arm and experimental arms. Our safety findings are consistent with recently published data from several studies. The maximum-dose tolerability study, HIGHRIF1 (NCT01392911), found no SAEs among participants who received rifampin doses up to 35 mg/kg over 14 days (25). The RIFATOX Phase II trial found that rifampin doses up to 20 mg/kg delivered over 16 weeks did not result in a significant increase in AEs (42). Finally, the more recent MAMS-TB-01 trial found that a rifampin dose of 35 mg/kg delivered as part of combination therapy over 12 weeks resulted in similar frequencies of grade 3 or higher AEs to standard therapy (26). Taken together, there is a growing body of evidence from controlled studies to suggest that concerns about the toxicity of rifampin may have taken on too much importance – relative to efficacy. In a future publication, we plan to pool data from this trial with those from another Phase II trial of high-dose rifampin conducted by PanACEA, HIGHRIF2 (NCT00760149) (27), with the goal of improving statistical power for efficacy and safety evaluations.

In summary, this is the first controlled trial to show dose- and exposure-response of higher doses of rifampin on sputum culture sterilization under conditions of combination therapy. Rifampin doses of up to 20 mg/kg/day were safe compared to the standard dose. These findings support

reconsideration of currently recommended standard dosing guidelines and the continued investigation of higher doses of rifampin, beyond 20 mg/kg, for potential treatment shortening.

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Figure 1. Study flow for efficacy analyses.

*One patient had an indeterminate Hain result.

†Clinical or radiological signs suggestive of pericardial, pleural, or miliary TB.

‡Serum alanine aminotransferase > 2 times the upper limit of normal.

§Hemoglobin concentration < 7.0 g/dL or platelet count < 150,000/mm^3.

‖Screening was not completed in four patients due to the implementation of protocol-defined study halts, and in one patient due to an inoperative Hain machine.

CFU = colony forming units; ET = early termination; INH = isoniazid; LTFU = lost to follow up; PK = pharmacokinetics; RIF = rifampin; TB = tuberculosis.

Figure 2. Predictions of bacillary elimination for the three treatment arms derived from the partial likelihood model showing observed data (dark grey) and model predictions (light grey) above and below the limit of detection of colony counting, respectively.

Table 1. Participant characteristics by treatment arm.*

Characteristic	Rifampin Dose 10 mg/kg *N* = 60	Rifampin Dose 15 mg/kg *N* = 60	Rifampin Dose 20 mg/kg *N* = 60	Total *N* = 180
Age (years), median (IQR)	24 (21-37)	25 (20-35)	27 (22-37)	25 (21-37)
Female	21 (35.0)	19 (31.7)	26 (43.3)	66 (36.7)
Weight (kg), median (IQR)†	53.5 (50.6-59.6)	55.4 (49.2-60.5)	54.9 (50.3-61.7)	54.1 (50.5-60.8)
BMI (kg/m^2), median (IQR)†	21.2 (19.2-23.3)	21.2 (19.5-23.9)	21.4 (19.9-24.2)	21.2 (19.6-23.7)
Cavitary disease (*n* = 178)	23 (39.0)	22 (37.3)	21 (35.0)	66 (37.1)
HIV positive	2 (3.3)	2 (3.3)	1 (1.7)	5 (2.8)
Diabetes (*n* = 179)	0 (0)	0 (0)	1 (1.7)	1 (0.6)
Smear grade at baseline				
++	32 (53.3)	24 (40.0)	31 (51.7)	87 (48.3)
+++	28 (46.7)	36 (60.0)	29 (48.3)	93 (51.7)
Baseline log_{10}CFU/mL, median (IQR) (*n* = 175)	5.0 (4.4-5.8)	5.0 (4.5-6.2)	5.1 (4.6-5.8)	5.0 (4.5-5.9)
Baseline TTP (days), median (IQR)	4.3 (1.6-5.0)	4.0 (0.1-5.2)	4.4 (0.1-5.0)	4.3 (0.1-5.0)
$MIC_{99.9}$, median (IQR)	0.2 (0.1-0.2)	0.2 (0.1-0.3)	0.2 (0.1-0.2)	0.2 (0.1-0.2)
$AUC_{0-6}/MIC_{99.9}$, median (IQR) (*n* = 168)	115.7 (59.1-197.6)	202.0 (144.1-460.3)	284.4 (175.3-399.2)	193.8 (112.0-344.4)
Rifampin dose (mg), median (IQR)	450 (450-600)	900 (600-900)	975 (750-1200)	750 (600-900)

Definition of abbreviations: AUC, area under the plasma concentration-time curve; BMI, body mass index; CFU, colony forming units; HIV, human immunodeficiency virus; MIC, minimum inhibitory concentration; TTP, time-to-positivity in BACTEC MGIT 960.

* Values shown are number (%) unless otherwise specified.

† Values for weight and BMI shown were those obtained at the randomization visit.

Table 2. Decrease in viable CFU counts of *M. tuberculosis* by rifampin dose or exposure to rifampin.

Dose/Exposure Variable	*N*	$\Delta\log_{10}$ CFU/mL/day	95% CI*	*P* value
5 mg/kg increase in rifampin dose				
mITT population	174	-0.011	-0.025 – 0.002	0.230
PP population	132	-0.022	-0.046 – -0.002	0.022
1 log increase in rifampin $AUC_{0\text{-}6}$				
mITT population	163	-0.001	-0.003 – 0.001	0.750
PP population	126	-0.017	-0.029 – -0.007	0.011
1 log increase in rifampin $AUC_{0\text{-}6}/MIC_{99.9}$				
mITT population	163	-0.002	-0.005 – 0.002	0.330
PP population	126	-0.010	-0.021 – 0.000	0.053

Definition of abbreviations: AUC, area under the plasma concentration-time curve; CFU, colony forming units; CI, confidence interval; mITT, modified intention-to-treat; MIC, minimum inhibitory concentration; PP; per-protocol.

* 95% CI were obtained using the sandwich estimator.

Table 3. Secondary efficacy outcomes.*

Outcome	Rifampin Dose 10 mg/kg *N* = 60	15 mg/kg *N* = 60	20 mg/kg *N* = 60	Total *N* = 180
Culture conversion in Löwenstein-Jensen medium at 8 weeks				
Converted	46 (76.7)	44 (73.3)	45 (75.0)	135 (75.0)
Did not convert	3 (5.0)	5 (8.3)	7 (11.7)	15 (8.3)
Contaminated week 8 cultures	4 (6.7)	1 (1.7)	0 (0)	5 (2.8)
Week 8 cultures not available	7 (11.7)	10 (16.7)	8 (13.3)	25 (13.9)
Early discontinuation	6 (10.0)	9 (15.0)	8 (13.3)	23 (12.8)
Lost to follow up	1 (1.7)	1 (1.7)	0 (0)	2 (1.1)
Treatment outcome at 12 months				
Recurrence-free cure	44 (73.3)	46 (76.7)	46 (76.7)	136 (75.6)
Treatment failure	3 (5.0)	1 (1.7)	1 (1.7)	5 (2.8)
Recurrence after cure	3 (5.0)	1 (1.7)	2 (3.3)	6 (3.3)
Relapse[†]	2 (3.3)	0 (0)	0 (0)	2 (1.1)
Reinfection[‡]	0 (0)	1 (1.7)	0 (0)	1 (0.6)
Recurrence[§]	1 (1.7)	0 (0)	2 (3.3)	3 (1.7)
Death	0 (0)	0 (0)	0 (0)	0 (0)
Outcome not evaluable	10 (16.7)	12 (20.0)	11 (18.3)	33 (18.3)
Early discontinuation	8 (13.3)	11 (18.3)	10 (16.7)	29 (16.1)
Lost to follow up	2 (3.3)	1 (1.7)	1 (1.7)	4 (2.2)

*Values shown are No. (%).

[†]2 patients had relapse diagnosed by identical pre-treatment and post-treatment *M. tuberculosis* isolates, with 24/24 matching MIRU-VNTR loci.

[‡]1 patient had reinfection diagnosed by nonidentical pre-treatment and post-treatment *M. tuberculosis* isolates, with 9/20 matching MIRU-VNTR loci.

[§]Recurrent tuberculosis was diagnosed without positive culture (and without MIRU-VNTR) in 3 patients: 2 were diagnosed by a positive sputum smear, and 1 was diagnosed clinically.

Table 4. Participants experiencing grade 2 or higher rifampin-related adverse events and hepatic adverse events during the safety period, by treatment arm.*

	Rifampin Dose			
Variable	10 mg/kg *N* = 60	15 mg/kg *N* = 60	20 mg/kg *N* = 60	*P* value
≥ 1 grade 2+ RIF-related AE	26 (43.3)	31 (51.7)	23 (38.3)	0.7092†
Time to first grade 2+ RIF-related AE (days), median (IQR)	29.5 (14-39)	26 (9-42)	25 (13-37)	0.3610‡
≥ 1 grade 2+ hepatic RIF-related AE	16 (26.7)	14 (23.3)	14 (23.3)	0.6645†
Time to first grade 2+ RIF-related hepatic AE (days), median (IQR)	31.5 (14-40.5)	36.5 (26-57)	42.5 (26-63)	0.8357‡

Definition of abbreviations: AE, adverse event; RIF, rifampin.

* Values shown are No. (%) unless otherwise specified. The safety period was defined as 12 weeks after randomization or 4 weeks after the last experimental rifampin dose, whichever occurred later.

† One-sided Cochran-Armitage test for trend with 5% significance.

‡ Global log-rank test.

Table 5. Participants experiencing serious adverse events by treatment arm.*

Variable	Rifampin Dose 10 mg/kg *N* = 60	15 mg/kg *N* = 60	20 mg/kg *N* = 60	*P* value†
≥ 1 SAE during entire study	2 (3.3)	1 (1.7)	5 (8.3)	0.0919
≥ 1 SAE during safety period‡	1 (1.7)	1 (1.7)	3 (5.0)	0.1333
≥ 1 RIF-related SAE during safety period‡	1 (1.7)	1 (1.7)	2 (3.3)	0.2679

Definition of abbreviations: RIF, rifampin; SAE, serious adverse event.

* Values shown are No. (%).

† One-sided Cochran-Armitage test for trend with 5% significance.

‡ The safety period was defined as 12 weeks after randomization or 4 weeks after the last experimental rifampin dose, whichever occurred later.