TITLE

Population Pharmacokinetic and Pharmacodynamic Study of Efficacy and Safety of High-Dose Rifapentine and Moxifloxacin for Treatment of Tuberculosis in the Study 31 Treatment Trial: Intensive PK Sampling

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Statement of Compliance

This trial will be conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice E6 (ICH-GCP), U.S. Code of Federal Regulations 45 CFR 46 and 21 CFR, and applicable site-specific regulatory requirements.

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Protocol Summary

The Tuberculosis Trials Consortium (TBTC) phase 3 treatment trial, Study 31, will investigate the efficacy and safety of daily rifapentine (1200 mg daily) with or without moxifloxacin as part of multidrug treatment regimens for drug-sensitive pulmonary TB. The proposed study (Study 31 PK/PD) will examine the population pharmacokinetics and pharmacodynamics (PK/PD) of high-dose daily rifapentine with and without moxifloxacin given for 17 weeks. Two different PK sampling procedures are required for the population PK/PD assessments involving rifapentine and moxifloxacin: (1) intensive sampling of 6 samples/participant on one occasion plus subsequent sparse sampling for a subset of Study 31 participants who are invited to co-enroll in Study 31 PK/PD; and (2) sparse sampling of 2-3 samples/participant for all other Study 31 trial participants (these data will be collected as part of the Study 31 treatment protocol). Herein, we describe the PK sampling to be conducted among those Study 31 participants who are co-enrolled to Study 31 PK/PD (n=60). Intensive PK sampling is needed in some participants to estimate the population PK model parameters with no bias and satisfactory precision (relative standard error < 20%). PK and outcomes data from all participants in Study 31 will be merged to build the population PK/PD models to evaluate PK/PD parameters. Details regarding these planned analyses are also provided in this Study 31 PK/PD protocol.

Primary Objectives:

1. Characterize the population pharmacokinetics of rifapentine and 25-desacetyl rifapentine, using sparse PK data from Study 31 and intensive PK data from Study 31 PK/PD. Using the population PK model, determine post-hoc Bayesian estimates of individual-level PK parameters.

2. Examine the relationship between rifapentine PK parameters of interest and treatment efficacy. PK parameters will include area under the concentration time curve (AUC_{0-24}), peak concentration (C_{max}), time above the mean inhibitory concentration (MIC), and AUC/MIC. The treatment outcome of interest will be time to culture conversion and time to treatment failure or relapse.

Secondary Objectives:

3. Among the Study 31 participants in the lowest 10% for rifapentine AUC_{0-24}, examine the PK/PD effect on culture conversion of sputa after completion of 4 months of daily rifapentine therapy.

4. Examine the relationship between safety outcomes (Grade 3 or higher adverse events) and rifapentine PK parameters (AUC_{0-24}, C_{max}, AUC_{0-24}/MIC and time above MIC).

5. Characterize the population PK of moxifloxacin, and then estimate moxifloxacin AUC_{0-24} and Cmax when moxifloxacin is administered with rifapentine given at a daily dose of 1200 mg.

6. Examine the relationships between moxifloxacin PK and treatment outcomes (as described in objective 2 for rifapentine) and moxifloxacin PK and safety (as described in objective 4 for rifapentine).

Design:

In Study 31 PK/PD, among 60 participants with tuberculosis enrolled in a rifapentine-based treatment arm of Study 31, PK data will be collected on two occasions. At TBTC sites that have the capacity to perform this activity, participants will have 6 scheduled PK samples per participant collected to measure rifapentine (with or without moxifloxacin) concentrations over approximately 24 hours. In addition among these 60 participants, 2 to 3 scheduled PK samples will be obtained on a second "late" sampling at > 14 days after the first PK sampling. Participants who enroll in this PK/PD protocol (for intensive and late PK sampling) will satisfy the obligation for rifapentine and moxifloxacin PK sampling. Participants in this PK/PD study will not undergo another "sparse" PK sampling for rifapentine as part of Study 31 protocol. Participants treated with rifampin-based therapy are excluded from this PK/PD study.

A sample informed consent document intended only for the 60 participants who will participate in this intensive PK study is attached to this protocol. Informed consent for sparse PK sampling for other participants enrolled in the Study 31 treatment trial is incorporated into the Study 31 protocol consent form.

Inclusion Criteria for Intensive Pharmacokinetic Sampling for Participants Enrolled in Study 31:

- Age 18 years or greater
- Enrolled in TBTC Study 31
- Randomized to receive one of the rifapentine treatment regimens.
- Willingness to be sampled 6 times during 1 PK sampling session and 2 - 3 times during another PK sampling session at an outpatient clinic, a clinical research center, or a hospital.
- Written informed consent given for the Study 31 PK/PD study

Exclusion Criteria for Intensive Pharmacokinetic Sampling for Participants Enrolled in TBTC Study 31:

- Hematocrit < 25% most recent value, measured within 30 days before PK/PD study enrollment.

1 KEY ROLES

Funding Agencies:
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2 BACKGROUND INFORMATION

2.1 Rifapentine

Rifapentine is approved by the United States Food and Drug Administration for treatment of drug-susceptible pulmonary TB based on an open-label prospective randomized phase 3 study of 722 participants with pulmonary TB [Priftin, 2014]. Rifapentine has a longer half-life than rifampin, but both drugs inhibit bacterial RNA synthesis by binding to the β-subunit of DNA-dependent RNA polymerase.

Rifapentine Pharmacokinetics

With once-weekly treatment in participants with pulmonary TB, mean plasma $AUC_{0\text{-}inf}$ was 296, 410, and 477 µg*h/mL after 600, 900, and 1200 mg doses administered without food, and Cmax was 12, 15, and 19 µg/mL [Weiner et al., 2006]. The bioavailability of rifapentine was 70% in healthy adult volunteers who were given a single 600-mg dose [Keung et al, 1998]. Food (total, 850 calories 33 g protein, 55 g fat, and 58 g carbohydrate) increases $AUC_{0\text{-}inf}$ by 43% and Cmax by 44% compared with fasting conditions [Priftin, 2014]. Rifapentine and its 25-desacetyl metabolite are 98% and 93% protein-bound in serum, primarily to albumin. Rifapentine is metabolized to 25-desacetyl rifapentine by an esterase enzyme present in the liver and blood. The half-life of rifapentine is 14 to 17 hours and the half-life of 25-desacetyl rifapentine is 13 hours. Rifapentine is excreted in bile and eliminated in feces, and < 10% rifapentine is excreted unchanged in urine. The microbiologically active metabolite contributes 40% of the overall activity of the drug. The MIC of rifapentine against *M. tuberculosis* is 0.05 µg/mL (0.25 µg/mL for 25-desacetyl rifapentine) [Priftin, 2014]. Single-dose rifapentine PK parameters are similar in healthy females and males [Thomson, 2014].

Clinical Trials of Rifapentine

The TBTC performed phase 2 studies to assess the antimicrobial safety and efficacy of daily rifapentine administered with isoniazid, pyrazinamide, and ethambutol for pulmonary TB treatment. In Study 29, adults (n = 531) who had sputum-smear-positive pulmonary TB were randomized to receive rifapentine 10 mg/kg/dose or rifampin 10 mg/kg/dose without food, 5 days per week for 8 weeks, with isoniazid, pyrazinamide, and ethambutol [Dorman et al, 2012]. This study showed no significant difference in antimicrobial activity between regimens, based on the surrogate marker of culture status at completion of the intensive phase (culture conversion on solid media: rifampin group, 83%; rifapentine group, 86%) (culture conversion in liquid media: rifampin group, 65%; rifapentine group, 68%). The rifapentine regimen was well tolerated, and similar proportions of participants between groups discontinued the assigned treatment overall (rifampin group, 16%; rifapentine group, 15%) or because of toxicity (rifampin group, 1.2%; rifapentine group, 1.5%). There were no differences in proportions of participants between treatment groups who had a serious adverse event related to study treatment (rifampin group, 0.4%; rifapentine group, 1.1%) or type or severity of adverse events between groups. The investigators concluded that the rifapentine regimen given on an empty stomach 5 days/week for 8 weeks was safe and well tolerated but not significantly more active than rifampin-based therapy.

A subsequent dose-ranging study to determine the optimal dose of daily rifapentine during the first 8 weeks of TB treatment was performed by the TBTC. In Study 29X, adults (n = 331) with sputum-smear-positive pulmonary TB were randomized and received or rifampin (10 mg/kg/dose) or rifapentine (10, 15, or 20 mg/kg/dose; maximum dose, 1500 mg) given with a high fat meal daily (7 days per week) for 8 weeks, in addition to isoniazid, pyrazinamide, and ethambutol. At completion of the intensive phase, negative cultures on solid media were noted in 52 of 64 subjects in the rifampin group (81%); 62 of 67 subjects in the rifapentine 10 mg/kg group (93%; not significant); 59 of 66 subjects in the rifapentine 15

mg/kg group (89%; not significant); and 54 of 57 subjects in the rifapentine 20 mg/kg group (95%; $P \leq .05$). Negative cultures in liquid media in the modified intention-to-treat analysis group occurred in 36 of 64 subjects in the rifampin group (56%); 50 of 67 subjects in the rifapentine 10 mg/kg group (75%; $P \leq .04$); 46 of 66 subjects in the rifapentine 15 mg/kg group (70%; not significant); and 47 of 57 subjects in the rifapentine 20 mg/kg group (83%; $P \leq .01$). High-dose daily rifapentine in combination with standard anti-TB drugs was well tolerated and highly active in surrogate bacteriologic tests (Dorman et al. 2015).

In the treatment trials 29 and 29X, the population PK properties of rifapentine were characterized in 415 participants. Rifapentine oral clearance did not significantly change with weight (Savic et al, manuscript in preparation). Rifapentine bioavailability decreased with greater rifapentine doses and the increase in exposure was less than dose-proportional. Median exposures at steady state of rifapentine AUC_{0-24} were 292, 474, and 579 µg*h/mL, respectively, for 600, 900, and 1200 mg daily doses. Because rifapentine clearance was not weight-dependent, a level rifapentine treatment dose (that is, a mg rather than a mg/kg dose) is recommended for adults. Rifapentine 1200 mg daily is incorporated into the Study 31 treatment trial protocol. Because food taken with rifapentine study doses significantly increased rifapentine exposure, it is recommended in Study 31 that a meal be taken prior to rifapentine study doses.

An important knowledge gap in TB clinical trials is how to efficiently and economically assess new drug efficacy, as biomarkers now commonly used in phase 2 trials have had varying success in predicting drug efficacy in phase 3 trials (Horne et al. 2010). However, optimal use of a drug can be achieved through population pharmacokinetic-pharmacodynamic (PK/PD) studies that combine pharmacokinetic properties of a drug and efficacy outcomes of treatment. In TBTC Study 29-29X PK/PD, the relation between rifapentine exposure and response by time to conversion in sputum cultures was established.

In these analyses, the efficacy of rifapentine was exposure-dependent (Savic et al, manuscript in preparation). Using maximum inhibitory effect (Emax) in a time-to-event model, a highly significant rifapentine exposure-response relationship was observed. With rifapentine $AUC_{0-24} > 350$ µg*h/mL, the percentage of participants with culture conversion of sputa from positive to negative in liquid media at 2 months of rifapentine treatment was modeled to be 74% and with rifapentine $AUC_{0-24} < 300$ µg*h/mL (“low rifapentine AUC) to be 55%. In summary, adequately high rifapentine exposure resulted in better responses, and large cavity size in poorer responses (Savic et al, manuscript in preparation).

The TBTC Study 31 is a phase 3, multicenter, international, randomized, controlled, open-label, 3-arm, non-inferiority trial that will enroll newly diagnosed, previously untreated participants with pulmonary TB. Two investigational regimens will be evaluated to determine if the duration of treatment for drug-susceptible pulmonary TB can be reduced compared to a standard rifampin-containing six month treatment regimen. In one investigational arm, the efficacy of the single substitution of rifapentine for rifampin for the 17 week regimen will be assessed. The second investigational arm will evaluate a rifapentine-containing regimen that also substitutes moxifloxacin for ethambutol and continues moxifloxacin for 17 weeks. The Study 31 primary efficacy endpoint is TB disease-free survival at 12 months after study treatment assignment. In addition, time to culture conversion will be assessed. The primary safety endpoint is the proportion of participants with grade 3 or higher adverse events during study drug treatment. This PK/PD Study is a component of TBTC Study 31.

2.2 Moxifloxacin

Moxifloxacin Pharmacokinetics

Moxifloxacin is a fluoroquinolone that has potent activity against *M. tuberculosis*. Moxifloxacin is well absorbed and has 90% bioavailability [Ballow et al., 1999]. The PK parameters are linear from 50 to 800 mg (single dose) and ≤ 600 mg (once daily dosing) over 10 days) [Stass et al., 1998]. Steady state is reached within 3 days [Stass et al., 2001]. The mean ± SD Cmax and AUC_{0-24} values at steady state with a 400-mg once-daily dosage regimen are 4.5 ± 0.5 µg/mL and 48 ± 3 µg*h/mL [Sullivan et al., 1999]. Trough plasma concentration at steady state (400 mg once daily) is 1.0 ± 0.1 µg/L. The time of C_{max} (T_{max}) is 1 to 3 hours. The mean plasma half-life is 12 ± 3 hours. Coadministration with food may slightly prolong T_{max} and reduce Cmax by 16%, but these effects are not clinically important. Administration with yogurt [Stass, Kubitza, 2001] or a high fat meal [Lettieri et al., 2001] did not significantly affect the AUC. However, coadministered with aluminum-, magnesium-, or calcium-containing antacids markedly reduced oral bioavailability of fluoroquinolones.

Moxifloxacin is 50% bound to plasma proteins. It is widely distributed, with some tissue concentrations in excess of plasma levels [Soman et al., 1999]. Moxifloxacin is metabolized by glucuronide and sulfate conjugation. The sulfate conjugate (M1) accounts for 38% oral dose and is excreted in feces; 14% of an oral dose is converted to the glucuronide conjugate (M2) and is excreted in urine [Stass, Kubitza, 1999]. Peak plasma levels of M1 are < 10% and M2 are 40% parent drug levels. Much (45%) of an oral dose is excreted as the parent drug and 51% as known metabolites. Based on population PK modeling, moxifloxacin AUC_{0-24} in participants who have TB can be predicted with acceptable accuracy using limited sampling strategy [Pranger et al., 2011].

Rifampin induces the activity of the phase 2 enzymes glucuronosyltransferase and sulfotransferase [Burman et al., 2001]. In a PK drug interaction between rifampin and moxifloxacin, the moxifloxacin AUC_{0-24} decreased 27% (ratio of geometric mean, 73 [90% CI, 64 to 84]) with coadministration of rifampin at a dose of 600 mg daily. In a PK interaction study of 19 participants who had tuberculosis, moxifloxacin AUC_{0-24} and Cmax decreased when moxifloxacin was administered daily with rifampin and isoniazid compared with moxifloxacin alone (ratio of geometric mean AUC_{0-24}, 0.69 [90% CI, 0.65 to 0.74]; Cmax, 0.68 [90% CI, 0.64 to 0.73]) [Nijland et al., 2003]. With rifapentine dosing 3 times per week in a PK interaction study in healthy volunteers, moxifloxacin AUC_{0-inf} was decreased 17% [Dooley K, et al., 2008]. In the RIFAQUIN PK study with 28 adults who had pulmonary tuberculosis treated with a continuation-phase regimen of 400 mg moxifloxacin and 900 mg rifapentine twice weekly, or 400 mg moxifloxacin and 1200 mg rifapentine once weekly, median moxifloxacin AUC_{0-inf} with rifapentine treatment once weekly was decreased 9% or twice weekly was decreased 11% [Jindani et al., 2013]. These PK drug interaction studies indicate that moxifloxacin AUC_{0-inf} is decreased with increased frequency of rifamycin dosing (from once weekly up to daily dosing). The magnitude of reduction in moxifloxacin concentrations when it is given with rifapentine at a dose of 1200 mg daily is unknown.

Moxifloxacin for Tuberculosis Treatment

Two phase 2 TB clinical trials that have shown that substitution of moxifloxacin for ethambutol during the intensive phase of pulmonary TB treatment increases the bactericidal activity with multi-drug, intensive-phase regimen, as assessed by sputum culture conversions to negative after 2 month of treatment [Rustomjee et al., 2008; Conde et al., 2009]. In another study, treatment with a weekly regimen of rifapentine and moxifloxacin during the continuation phase of therapy (for a total TB treatment for 6

months) was not inferior to daily isoniazid plus rifampin; the efficacy of rifapentine plus moxifloxacin in this trial was important because once-weekly rifapentine with isoniazid (instead of moxifloxacin) was associated with a higher frequency of relapse and treatment failure [Tuberculosis Trials Consortium, 2002; Tam et al., 1998]. In the REMox phase 3 trial, randomized double-blind trial to test non-inferiority of a seventeen weeks of isoniazid, rifampicin and moxifloxacin supplemented by pyrazinamide for the first eight weeks (INH-arm) compared to standard 6 months of rifampin based regimen for tuberculosis, the number of participants classified as favorable in the control regimen per protocol was 467 (92%) and in the INH-arm 436 (85%) a difference of 6.1% (97.5% CI 1.7-10.5) [Gillespie SH et al. 2014]. In this trial, the moxifloxacin containing regimen was more bactericidal than the control regimen, but there was insufficient activity to permit a rifampin-moxifloxacin regimen to be shortened to 4 months. The relationship between moxifloxacin concentrations and TB treatment outcomes when moxifloxacin is given as part of high-dose rifapentine-based multidrug treatment for drug-sensitive TB is unknown. Further, the target exposure of moxifloxacin for treatment of TB has not been defined.

2.3 Rationale for Intensive and "Late" PK Samplings for Rifapentine at Two Different Occasions

Autoinduction has been described previously with daily dosing of rifamycins, including rifampin and rifapentine (Acocella el al, 1971, Savic et al, 2014). With autoinduction of metabolizing enzymes or transporters, both bioavailability and clearance can theoretically be affected. In a population PK model from healthy volunteers, rifapentine clearance appeared to be time-dependent, whereas time had a less significant effect on bioavailability (Savic et al, 2014). In addition, there was no clear relationship between dose and clearance, or dose and the effects of time on clearance. Further in this prior study, the time to maximal autoinduction with daily dosing could not be estimated as increases in clearance were seen up until the final PK sampling day after 14 days of dosing. PK sampling over longer dosing intervals is required to determine the time course of autoinduction and the change in exposures over time with repeated dosing.

Information from this PK study is needed to fill this knowledge gap, and to model the population PK model parameters without bias and with satisfactory precision (relative standard error < 20%). Reiterated simulations and re-estimations ("sse") of rifapentine data in Study 29-29X were performed to assess the optimal Study 31 PK/PD design for: (1) between-subject variability (BSV) and precision of the population PK parameters, and (2) the longitudinal component of rifapentine clearance by autoinduction. Uncertainty in parameter estimates (RSE) of <10% was considered acceptable for the population PK parameters and < 20% for the parameter describing autoinduction. These simulations indicated that for the parameter describing rifapentine auto-induction, it is important that multiple PK samplings are obtained, and that PK sampling occasions be time-balanced. If this is not performed, the uncertainty of the longitudinal change in clearance substantially increases, i.e. a protocol design with only one initial PK sampling is not able to identify longitudinal change in clearance with satisfactory precision, and leads to high uncertainty in parameter estimates. A parsimonious design that efficiently assesses longitudinal changes in clearance with adequate certainty and limited costs, will include the following features: (i) a minimum of 60 participants; (ii) intensive PK sampling (6 optimal samples/participant (times = 0.5, 3, 6, 9, 12, 24 hours) on at least one occasion; and (iii) late sampling with 2 to 3 PK samples at another, later occasion separated by a minimum of 14 days. In summary, this PK/PD Study is valuable because, it will allow a robust development of population PK model parameters for rifapentine and for moxifloxacin in presence of high-dose rifapentine, and evaluate the PK/PD relationships of study drugs with efficacy outcomes.

3. OBJECTIVES

Primary Objectives:

1. Characterize the population pharmacokinetics of rifapentine and 25-desacetyl rifapentine, using sparse PK data from Study 31 and intensive PK data from Study 31 PK/PD. Using the population PK model, determine post-hoc Bayesian estimates of individual-level PK parameters.

2. Examine the relationship between rifapentine PK parameters of interest and treatment efficacy. PK parameters will include area under the concentration time curve (AUC_{0-24}), peak concentration (C_{max}), time above the mean inhibitory concentration (MIC), and AUC/MIC. The treatment outcome of interest will be time to culture conversion and time to treatment failure or relapse.

Secondary Objectives:

3. Examine participants with low 10% rifapentine AUC_{0-24}, the PK/PD effect on culture conversion of sputa after completion of 4 months of daily rifapentine therapy.

4. Examine the relationship between safety outcomes (Grade 3 or higher adverse events) and rifapentine PK parameters (AUC_{0-24}, C_{max}, AUC_{0-24}/MIC and time > MIC).

5. Characterize the population PK of moxifloxacin, and then estimate moxifloxacin AUC_{0-24} and Cmax when moxifloxacin is administered with rifapentine given at a daily dose of 1200 mg.

6. Examine the relationship between moxifloxacin PK and treatment outcomes (as described in objective 2 for rifapentine) and moxifloxacin PK and safety (as described in objective 4 for rifapentine).

4 STUDY DESIGN

In Study 31 PK/PD, among 60 participants with tuberculosis enrolled in a rifapentine-based treatment arm of Study 31, PK data will be collected on two occasions. At TBTC sites that have the capacity to perform this activity, participants will have 6 scheduled PK samples per participant collected to measure rifapentine (with or without moxifloxacin) concentrations over approximately 24 hours. In addition among these 60 participants, a “late” sampling for 2 to 3 PK samples will be obtained on a second occasion at > 14 days after the first PK sampling. Participants who enroll in this PK/PD protocol (for intensive and late PK sampling) will satisfy the obligation for rifapentine and moxifloxacin PK sampling. Participants enrolled in this PK/PD study will not undergo “sparse” PK sampling for rifapentine as described in the Study 31

Protocol. Participants in Study 31 treated with rifampin-based therapy are excluded from this PK/PD study.

A sample informed consent document intended only for the 60 participants who will participate in this intensive PK study is attached to this protocol. Informed consent for sparse PK sampling for other participants enrolled in the Study 31 treatment trial is incorporated into the Study 31 protocol consent form.

5 STUDY POPULATION

Participants enrolled in the Study 31 treatment trial will be recruited from TBTC sites with capacity to perform intensive PK sampling. Subjects will be reimbursed for travel expenses to PK study visits, and otherwise compensated in accordance with standards determined by the study site.

5.1 Subject Inclusion Criteria

- Age 18 years or greater
- Enrolled in TBTC Study 31
- Randomized to receive one of the rifapentine treatment regimens.
- Willingness to be sampled 6 times during 1 PK sampling session and 2 - 3 times during another PK sampling session at an outpatient clinic, a clinical research center, or a hospital.
- Written informed consent given for the Study 31 PK/PD study

5.2 Criteria for Exclusion from Enrollment

- Hematocrit < 25% most recent value, measured within 30 days before PK/PD study enrollment.

6 ENROLLMENT

Sixty participants will be enrolled, 30 from the rifapentine treatment arm (regimen including rifapentine, isoniazid, pyrazinamide, ethambutol) and 30 from the rifapentine and moxifloxacin treatment arm (regimen of rifapentine, isoniazid, pyrazinamide, moxifloxacin). Participants should be enrolled after a minimum of 14 study drug doses (including directly observed therapy and self-administered doses). Participation in this component study of Study 31 will be counted as fulfilling all PK sampling requirements in Study 31.

7 STUDY PROCEDURES

7.1 Pharmacokinetic Sampling

With the intensive PK sampling procedures, blood samples will be obtained at 6 time points per participant over 23 to 25 hours. On a separate occasion > 14 days later, a PK sampling will be performed with 2 to 3 blood samples obtained per participant. Details regarding PK sampling are described in Section 8.1. An informed consent document for PK sampling (on 2 occasions - intensive and late) is described in Appendix 1 of this protocol.

7.2 Timing of Pharmacokinetic Sampling during Tuberculosis Treatment

The minimum number of study drug doses taken before the PK blood draw will be 14 (including both directly observed therapy (DOT) and self-administered doses). The preferable timing of the initial intensive PK sampling will be at the 2, 4 or 8 week study visit after initiating treatment in Study 31. However, if the dosing schedule or other factors do not permit sampling at any of these scheduled study visits, sampling may be performed any time after 14 study drug doses. An additional late PK sampling (2 to 3 samples/participant) will occur in participants enrolled in this study at 14 days or more after intensive PK sampling.

7.3 Eating in Relation to the Pharmacokinetic Study Reference Doses

Participants treated with rifapentine in Study 31 are requested to take rifapentine doses within one hour after eating a meal. For the PK reference doses, food intake should be similar to the food intake for other study doses and times relative to study drug dosing. This is important because we want drug exposures that are measured on the PK visit day to reflect drug exposures for participants over the course of the study. So, for example, if the participant regularly has food with study treatment, the participant should also have the same kind of food at the time of drug administration for PK sampling. If however the participant regularly fasts (does not take food) with study treatment, then the participant should fast at the time of drug administration for PK sampling. Water or another liquid will be permitted for the purpose of swallowing pills. The timing of food relative to the reference dose of study drugs and a brief description of any food and liquids consumed will be recorded on study Case Report Forms. Participants will abstain from alcohol for 48 hours before the reference dose of study drugs and until after the last PK specimen is collected.

7.4 Collection, Processing and Storage of PK Samples

Plasma will be divided into at least 3 aliquots and stored at the TBTC sites at < -70 degrees C until shipment for drug analyses. It is anticipated that 2 or more batch shipments of participant samples for analyses of study drug concentrations will be scheduled as described in the Manual of Operating Procedures (MOOP). The maximum amount of blood taken from each participant in this PK study will be 90 mL.

- The total amount of blood for intensive sampling will be 60 mL.
- The total amount of blood for late sampling will be up to 30 mL.

International shipments of samples are anticipated between study sites and the analysis laboratory.

7.5 Analyses of Study Drug Concentrations

Plasma rifapentine (and desacetyl-rifapentine) and moxifloxacin concentrations will be determined by a laboratory with validated assays for the study drugs. The intraday accuracy and intraday precision will be determined with quality control samples, which will be analyzed concurrently with each set of subject samples. The intraday accuracy and precision will be published.

7.6 Collection of Safety Data

All participants in Study 31 PK/PD will have information about adverse events collected as part of their participation in Study 31. In addition, any adverse events related to PK sampling procedures in Study 31 PK/PD will be collected and reported. All reportable adverse events encountered during the study will be recorded on standardized case report forms as outlined in the MOOP.

8 STUDY SCHEDULE

8.1 Schedule of Pharmacokinetic Blood Samplings

Intensive PK Sampling:

All PK blood samples will be collected following 4 consecutive daily study doses (of which the 3 consecutive doses immediately before PK sampling must be given by direct observation). The fourth rifapentine dose (Reference Dose #1) will be administered by DOT on the day PK sampling is to begin. The precise times of all four doses will be recorded on the case report form.

Six PK samples will be collected, as follows: ½ hour, then at 3, 6, 9, 12, and 24 hours after ingestion of Reference Dose #1 of study drugs.

Table 1. Intensive PK: Timing of Drug Administration Relative to Pharmacokinetic Sampling and Other Procedures Sampling

Procedure	**-1 hr.**	**0 Reference dose # 1**	**0.5 hr.**	**3 hr.**	**6 hr.**	**9 hr.**	**12 ± 1 hr.**	**24 ± 1 hr.**
Time (example)	7 - 8 AM	8 AM	8:30 AM	11 AM	2 PM	5 PM	8 PM	8 AM
Sample for concentration of study drugs	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Administration of study drugs	No	Yes	No	No	No	No	No	Yes (after 24 hr. PK sample)
Food	Yes							

Late PK Sampling:

This PK visit should be scheduled at least 14 days following the intensive PK sampling visit. Two to three PK samples will be collected over 5 to 8 hours. All PK blood samples will be collected in reference to 4 consecutive daily study doses (of which the 3 consecutive doses immediately before PK sampling must be given by direct observation). The first timed PK blood specimen will be obtained 24 hours (± 1 hour) after the third daily study dose and will be called "Reference Dose #2". After obtaining the first timed PK blood specimen, the 4th daily study dose called "Reference Dose #3" will be ingested. The second timed PK sample will be obtained 25 to 40 minutes after Reference Dose #3. The third timed specimen will be obtained 5 to 8 hours after ingestion of Reference Dose #3.

Table 2. Late PK Sampling: Timing of Drug Administration Relative to Pharmacokinetic Sampling and Other Procedures

Procedure	**- 25 hr.**	**- 24 hr. Reference PK Dose #2 1 hr. after food**	**- 1 hr. Food**	**PK sample obtained 24 ± 1 hr. after Reference Dose #2 and just prior to Reference Dose #3**	**Reference Dose #3**	**25 - 40 minutes**	**5 - 8 hr.**
Time (example)	7 - 8 AM	8 AM	7 - 8 AM	8 AM	8 AM	8:25 to 8:40 AM	1 to 4 PM
Sample for concentration of study drugs	No	No	No	Yes	No	Yes	Yes
Administration of study drugs	No	Yes	No	No	Yes	No	No
Food	Yes	No	Yes	No	No	No	No

Other Data to Collect on PK Sampling Days:

The following data will be recorded on admission for both PK sampling sessions: vital signs, weight, and Karnofsky score. Participants will be interviewed to obtain additional information about medical history, recent weight loss or gain, concomitant medications on the day before and days of PK sampling, gastrointestinal symptoms, and timing of meals and snacks relative to study drug dosing.

9 ASSESSMENT OF EFFICACY

Pharmacodynamic models will be employed to assess rifapentine and moxifloxacin PK parameters in relation to markers of mycobactericidal efficacy. Associations will be evaluated for significance between (1) rifapentine and moxifloxacin AUCs and peak concentrations and (2) bactericidal endpoints of time to stable conversion with solid and liquid media and time to treatment failure or relapse.

10 ASSESSMENT OF SAFETY

The safety associated with pharmacokinetic samplings will be reported as Adverse Events performed in TBTC Study 31, “Rifapentine-containing treatment shortening regimens for pulmonary tuberculosis: A randomized, open-label, controlled phase 3 clinical trial”. The PK/PD assessment of safety will assess the associations between (1) rifapentine and moxifloxacin AUCs and peak concentrations and (2) Adverse Events, Grade $\geq$ 3, reported in the Study 31 treatment trial.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

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Primary Objective 1: Robust population PK models for rifapentine can be developed using intensive plus later PK data from Study 31 PK/PD and sparse PK data from Study 31. From this model, individual-level PK parameters that are precise and accurate can be estimated and the time course of autoinduction for rifapentine can be described.

Primary Objective 2: Rifapentine exposure as measured by $AUC_{0\text{-}24}$ will be negatively associated with time to culture conversion, after adjusting for significant factors known to affect culture conversion. Further, low rifapentine concentrations will be a predictor of relapse.

Secondary Objective 3: Participants with the lowest 10% of rifapentine exposure in the Study 31 trial who have positive sputum cultures after 2 months of treatment will be cured after 4 months of rifapentine-based therapy.

Secondary Objective 4: Rifapentine PK parameter values will be associated with risk of adverse events.

Secondary Objective 5: Moxifloxacin exposures will be reduced when moxifloxacin is given together with rifapentine as compared to moxifloxacin alone among historical controls.

Secondary Objective 6: Moxifloxacin exposure as measured by $AUC_{0\text{-}24}$ will be negatively associated with time to culture conversion and with relapse. Moxifloxacin PK parameter values will not be associated with risk of adverse events.

11.2 Analysis Plan

Objective 1 - Rifapentine Population PK: Rifapentine PK parameters will be estimated with a nonlinear, mixed effects approach. Estimation of population PK parameters, interindividual variability, and interoccasional variability will be performed with NONMEM version 7 software (ICON, Dublin, Ireland) using the first-order conditional estimation method with ε-η interaction. Post hoc Bayesian estimates of individual AUC will be derived from the models (See Appendix 2 for detailed analyses plan). Changes over time in clearance with repeated dosing will be characterized to fully describe rifapentine autoinduction process.

Objective 2 - PK / Efficacy Analyses for Rifapentine: Development of a PK/PD model will use a parametric survival function time-to-event model with treatment efficacy endpoints of serial sputum cultures for time to culture conversion and time to treatment failure or relapse (See Appendix 2 for detailed analyses plan).

Objective 3 - Efficacy with Low Rifapentine Exposure: Participants with the lowest 10% of rifapentine AUC in the Study 31 trial and with positive sputum cultures after 2 months of treatment will convert to stable negative cultures after completion of 4 months of rifapentine-based treatment as assessed with the McNemar's test.

Objective 4 - PK / Safety Analyses for Rifapentine: PK-safety analysis will be performed as described by Plan et al. (2010) using a time to event variable, where the event will remain a graded outcome (Grade $\geq$ 3 Adverse Events from Study 31). This approach utilizes both time aspect of the event (time to safety event) and severity of event (grade).

Objective 5 - Moxifloxacin Population PK: Moxifloxacin PK parameters will be estimated with a nonlinear, mixed effects approach, similar to that described for Objective 1 above. To assess the drug interaction effect of rifapentine on moxifloxacin given at a dose of 400 mg once daily, post-hoc estimates of moxifloxacin AUC will be compared with a one-sample t-test with historical AUC values for healthy volunteers taking moxifloxacin at a dose of 400 mg once daily without a rifamycin (39.1 mcg*h/mL from historical trial data).

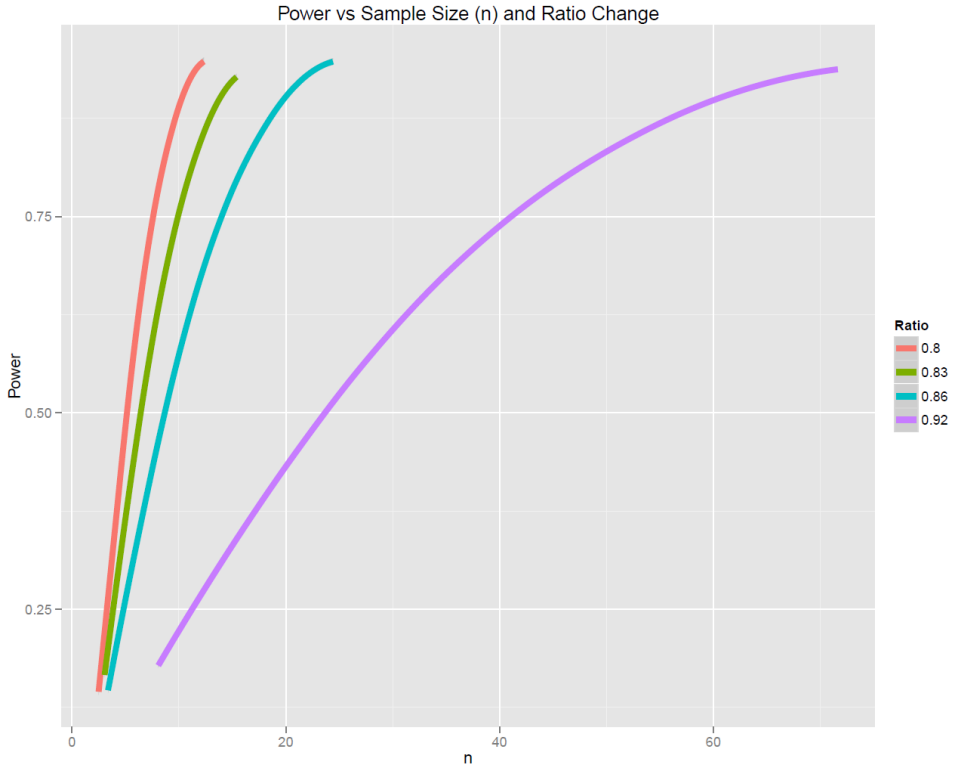
Objectives 6 - PK / Efficacy and PK / Toxicity Analyses for Moxifloxacin with Rifapentine: Similar analyses for moxifloxacin with rifapentine will be performed as described for rifapentine alone in Objectives 2 and 4.

11.3 Sample Size Considerations

Intensive PK sampling and late sparse PK sampling will be performed in Study 31 PK/PD. The Study 31 PK/PD study is powered to ensure that the PK of rifapentine can be fully characterized over time, taking into account autoinduction of clearance of this drug. That is, PK parameters are time-dependent and change over time with repeated dosing. PK data collected in Study 31 PK/PD will be combined with Study 31 parent study sparse PK data to build PK/PD models that assess PK-efficacy and PK-safety relationships. Having PK data from intensive PK sampling from Study 31 PK/PD will help ensure that the models are robust and that individual-level estimates of PK parameters are precise and accurate.

Power and sample size to characterize changes in rifapentine clearance over time among participants taking daily high-dose rifapentine therapy.

To robustly model the population PK model parameters without bias and with satisfactory precision, the longitudinal change of rifapentine clearance over treatment time will be characterized (see Section 2.2: Rationale for intensive and late PK samplings at 2 different occasions). For a sample size calculation with 60 participants in this study, PK data on two occasions will be obtained from an intensive and then late PK procedures. With the assumptions that the within participant coefficient of variation is 20% of rifapentine clearance, that the ratio of rifapentine clearance at baseline (after >2 weeks of therapy) divided by clearance at steady state is 0.92 (an 8% decrease), and that the Type I error is 0.05, a total of 53 participants with 2 sets of PK data will be required to achieve power of 85% with a paired t-test applied to the logarithm of the AUC values.



Power and sample size to assess the relation between rifapentine exposure ($AUC_{0\text{-}24}$) and efficacy by time to stable culture conversion of sputa in liquid cultures.

In Study 29-29X PK/PD, time to stable conversion was best described with Weibull model with increasing probability (hazard) of culture conversion with time. PK-based predictors were related to the hazard parameter (*P* < 0.001) and participants with high AUC or Cmax showed significantly decreased treatment time to achieve stable culture conversion (Savic et al, manuscript in preparation). Based on data in Study 29-29X PK/PD with the assumption of a hazard ratio of 1.35 for participants with the higher 70% to the lower 30% rifapentine $AUC_{0\text{-}24}$ and a Type I error of 0.05, a power of 87% is achieved by the log-rank test with 500 participants. To achieve the desired sample size, data from the 60 participants co-enrolled in the Study 31 PK/PD study will be combined with PK data from other participants in the Study 31 treatment trial.

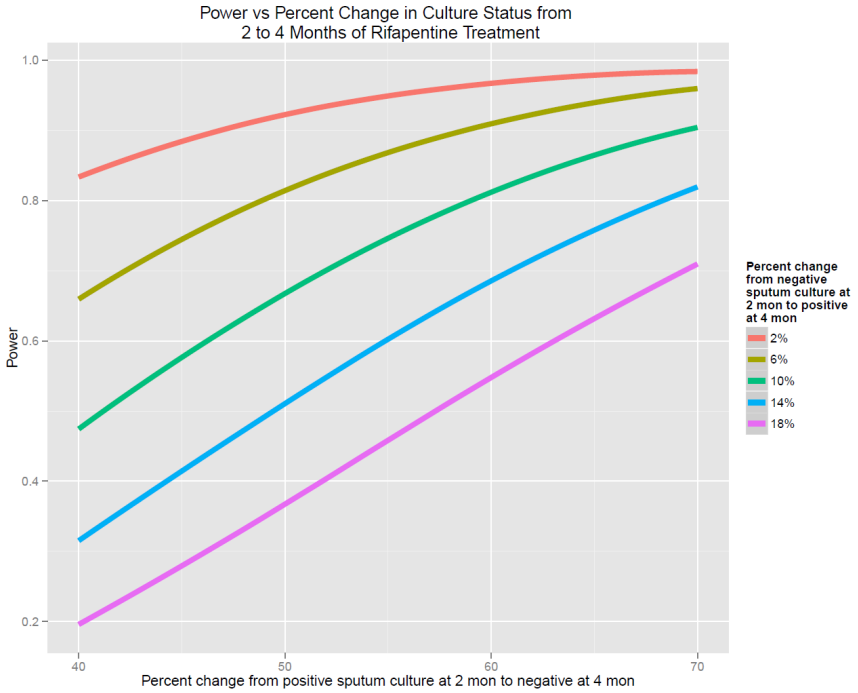
No. Study Participants	Power
200	49
300	66
400	78
500	87
600	92

Power to assess whether or not participants in Study 31 with the lowest 10% of rifapentine AUC_{0-24} and with positive sputum cultures at 2 months of therapy will have treatment success after completion of 4 months of rifapentine therapy

We hypothesize that those Study 31 participants with the lowest 10% of rifapentine AUC_{0-24} will convert sputum cultures in liquid media from positive for *M. tuberculosis* at 2 months of rifapentine treatment to negative after completion of 4 months of rifapentine treatment. We will use a McNemar's test to assess the transitions of positive and negative sputum cultures. The sample size assumptions are that: (a) the distribution of rifapentine AUC in Study 31 will be similar to TBTC Study 29X, i.e. of 550 participants treated with a daily dose of rifapentine 1200 mg taken with food in Study 31, 55 (10% of) participants will have a low rifapentine AUC (Savic et al, manuscript in preparation); (b) positive sputum cultures at 2 months of rifapentine treatment (as in the Study 29-29X PK/PD model) will occur in 45% of participants in the low rifapentine AUC group; and (c) that 3% of participants with low rifapentine AUC with negative sputum culture at 2 month treatment will have positive cultures after completion of 4 months of rifapentine treatment. With these assumptions, a McNemar's test will have 92% power to detect a 61% improvement from positive sputum cultures at 2 months to negative after 4 months of treatment. The null hypothesis is that there is no net improvement from 2 to 4 months. A contingency table of percent and number of participants with positive and negative cultures at 2 and 4 months of treatment is illustrated below.

Contingency table with 2 month (rows) and 4 month (columns) projections of culture results with rifapentine treatments. Delta improvement = 0.61 (X-axis in Figure below).

	Negative culture - after 4 months RPT treatment Number (percent)	Positive culture - after 4 months RPT treatment Number (percent)	Sum – Number (percent)
Negative culture - 2 month RPT	29 (52.7)	1 (1.8%)	30 (54.5)
Positive culture - 2 month RPT	15 (27.3)	10 (18.2)	25 (45.5)
Sum – Number (percent)	44 (80)	11 (20)	55 (100)



12 QUALITY CONTROL AND QUALITY ASSURANCE

Study staff will be trained in Good Clinical Practice and in performance of study procedures. The sponsor or the sponsor's delegate will ensure that everything is in place for the trial to start, the study file contains all the essential documents, and study staffs understand procedures and their roles and responsibilities. The study will be conducted in accordance with the protocol and study-specific procedures manuals.

12.1 Local quality control

Each site will have a written plan for local quality control including data quality management.

12.2 External monitoring

External monitoring will be conducted periodically to ensure the safety and proper execution of this PK study by a contract research organization (CRO). Direct access to data at each site will be required for the purposes of monitoring and audit, and this will be made explicit in the consent form. Local investigators and their institutions will provide direct access to source documents and data for trial-related monitoring, audit, and regulatory inspections.

External monitoring will be conducted according to a written manual of procedures. Adverse events specifically associated with PK sampling procedures in Study 31 PK/PD will be reported via the procedures for the parent Study 31 treatment trial. Monitoring will focus on ensuring that the following study activities are conducted per the protocol and associated documents: consent procedures, enrollment, correct timing and administration of study medications, correct implementation and accurate reporting of study procedures, appropriate reporting of adverse events, accurate completion of case report forms, and timely and accurate data entry. Additional activities or study elements may be monitored as needed.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

This study will be conducted in conformity with the ethical standards set out in the latest version of the Declaration of Helsinki.

13.1 Institutional Review Board

Each participating institution will provide for the review and approval of this protocol and the associated informed consent document by an appropriate Institutional Ethics Committee (IEC) or Institutional Review Board (IRB). Any amendments to the protocol or consent materials must also be approved before they are placed into use.

The investigator will promptly report to the institutional review board all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make changes in the research without ethics committee/institutional review board approval, except where necessary to eliminate immediate hazards to human subjects.

13.2 Informed Consent Process

Only individuals who provide written informed consent will be enrolled in this study. Written informed consent is required before any study-specific procedures are performed. Potential participants will have the conditions of the study explained to them, including potential harms and benefits, the nature and timing of study procedures, alternatives to study participation, that study participation is voluntary, that a decision to not participate in the study will not affect the quality of their future medical care, and that they may withdraw from participation at any time. The investigator or designee will ensure that the purpose of the study is explained to the participant and that written consent is obtained before participation in the study. The information in the Informed Consent document will be translated into relevant local languages. Literate individuals will be provided with a language-appropriate document to read; illiterate individuals (i.e. individuals who speak and understand, but do not read and write, the language in which the consent discussion is conducted) will have the contents of the document explained to them by a trained study staff member; such individuals can be enrolled by 'making their mark' on the consent document. Potential participants will have the opportunity to ask questions of the site investigator or delegate, and to discuss participation with their family and/or friends or think about the study prior to deciding whether or not to participate. A copy of the signed informed consent document will be given to the participant for his/her records. The investigator will retain a copy of the signed consent form, which may be inspected upon request by the monitor or auditor; this will be the original form unless otherwise specified by the policies of the institution where the research is conducted.

13.3 Subject Confidentiality

All records identifying the participant will be kept confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available without sufficient de-identification procedures.

Participant names will not be supplied to the sponsor. All study samples will be identified by a code only. All study documents and forms will be identified by a code only. All paper study records will be stored in a locked office and electronic study records will be stored on password-protected computers; only designated trained study staff will have access to study records. Transmission of electronic records to the sponsor will occur through a web-based data entry application that conforms to the Federal Information Security Management Act, or using a secure CDC File Transfer Protocol (FTP).

The study monitors, other authorized representatives of the sponsor, and regulatory authorities may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records, primary laboratory data, and pharmacy records for study participants; this information will be provided to participants during the Informed Consent process. The clinical study site will permit access to such records.

13.4 Study Discontinuation

If the Study 31 treatment trial or a study arm is closed, resulting in closing or modification of this PK/PD study, then all involved ethics committees should be notified. If a site is closed, then the local IEC/IRB and the CDC IRB should be notified.

14 DATA HANDLING AND RECORD KEEPING

ICH-GCP requirements for data documentation will be followed.

Data handling and record keeping will be performed in accordance with a study MOOP. Briefly, information from source documents will be recorded on study-specific case report forms, which will be entered into the study electronic information system. The study electronic information system will be programmed to maintain an audit trail, perform consistency checks, and generate reports of missing/inconsistent data. After study completion, de-identified data that can be legally released to the public may be released through a public-use data set after the data are evaluated for quality and confidentiality and shared with any partners, per CDC's policy on data sharing.

The study file and source documents will be retained until the sponsor gives notification.

15 PUBLICATIONS AND DISSEMINATION OF STUDY RESULTS

The study lead investigators and the TBTC Publications and Presentations committee must approve the use of any coded study data for the purposes of publication or presentation in advance. Any proposal for collection of additional data or analysis of study data must be agreed to in advance by the study lead investigators and the protocol team. The preparation of and authorship of publications arising from this study will be in accordance with the TBTC Bylaws.

These criteria will not apply to public-use data that have been made available in accordance with CDC's policy on data sharing. Persons who use publicly available data will be asked to acknowledge the TBTC and the S31 Protocol Team.

Updates on the progress of the trial will be presented at periodic TBTC meetings. Additional dissemination of results will be through the press, national governments at meetings and international organizations at conferences. Overall (aggregate) study results will be shared with study participants through mechanisms and materials reviewed and approved by the TBTC Community Research Advisors Group.

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SUPPLEMENT/APPENDICES

Appendix 1.
Consent Form – See separate attachment

Appendix 2. Detailed Analyses Plan for Population Pharmacokinetic and Pharmacodynamic Models

Rifapentine and moxifloxacin PK parameters will be estimated with a nonlinear, mixed effects approach. The model will be developed with PK data from (a) 60 participants who will undergo intensive sampling (6 samples/ participant) after ≥ 14 daily doses and (b) ≥ 1500 participants who will have sparse and "late" sampling (2 or 3 samples/ participant). It is anticipated that the PK models will use ≥ 3800 data points for rifapentine and metabolite (25-desacetyl rifapentine) from 1550 adults. A moxifloxacin model will use ≥ 1900 data points from ≥ 750 participants. Concentration values below the lower limit of quantification will be included in the PK evaluation and appropriate methodology for dealing with censored data will be implemented. Estimation of population PK parameters, interindividual variability, and interoccasional variability will be performed with NONMEM version 7 software (ICON, Dublin, Ireland) using the first-order conditional estimation method with ε-η interaction.

Model building will be divided into several steps. A base rifapentine model will be developed, metabolite data will be introduced, a metabolite model will be developed, and the base rifapentine model will be adjusted. The complete data will be modeled simultaneously, and parameters will be re-estimated for both rifapentine and metabolite. If needed, other available algorithms (NONMEM 7) will be used, with emphasis on stochastic algorithms (Monte Carlo Parametric Expectation Maximization, Stochastic Approximation Expectation Maximization). A stepwise procedure will be used to determine whether a 1-, 2-, or multi-compartment model will best fit the data under the principle of parsimony. Building on previous information about rifamycin PK, a 1-compartment model and transit-compartment model for absorption will be attempted with adjustments based on fit [Sullivan et al., 1999; Savic et al, 2014]. Additional absorption models will be tested, including Erlang absorption model and first-order absorption model with a lag time. Residual error will be modeled as a proportional, additive, or combined error model. Before the covariate model building procedure, all parameters will be allometrically scaled to body weight to account for size-dependent differences in PK and it will be retained in the model if allometric scaling is significant. Additional covariates to be tested for inclusion in the structural model will include dose, age, sex, HIV status, food, and treatment regimen. The effect of each covariate on the PK parameters will be tested sequentially using a stepwise covariate model building procedure with forward inclusion (P = .05) and backward deletion (P = .01) for covariate retention. All covariates that show an effect on the parameters will be evaluated again by comparison of the full model (with all factors included) with a model from which each factor is deleted sequentially. Developing this model to analyze data will provide information about whether any of these covariates alter the absorption, volume of distribution, or clearance of the study drugs. Goodness of fit in the model building process will be assessed using standardized procedures (Xpose 4, Uppsala University, Uppsala, Sweden). The final model will be evaluated extensively with several computer intensive methods, including visual and numeric predictive checks, nonparametric bootstrapping, and Normalised Prediction Distribution Errors.

Development of the PKPD model

In order to describe the time to the stable culture conversion, a parametric survival function was used (according to the equation that follows):

$$S_t = e^{-\int_0^t h(t)d(t)}$$

The hazard is h(t), and the 'survival' S(t) is a function of the cumulative hazard within the time interval between the time zero and the time t describing the probability of not converting culture to negative status within this interval. The base model was developed by exploring different functions for the hazard h(t), starting from a simple time independent constant hazard and then gradually progressing to more complex functions, including Weibull function as shown in the Equation 2, where h0 represents baseline hazard at time 0, γ is a shape parameter and t is time.

$$h_t = h_0 * \gamma * (h_0 * t)^{\gamma-1}$$

Model building was guided by the likelihood ratio test, diagnostic plots, and internal model validation techniques, including visual and numeric predictive checks. Covariates were identified by an automated procedure with Stepwise Covariate Model software (PsN, SourceForge, Slashdot Media, San Francisco, CA), and linear and nonlinear relations were tested stepwise with forward inclusion (difference in objective function values (ΔOFV), 5.99; P ≤ .01 for 1 degree of freedom) and backward exclusion (ΔOFV, 10.83; P ≤ .001 for 1 degree of freedom). With categorical covariates, ΔOFV at the noted P values may have varied with the degrees of freedom. The final model contained covariates that met the predefined statistical criteria and were retained because of clinical relevance. The covariates tested in the model were age, sex, weight, race, HIV status, and body mass index (BMI). The absorption rate constant (ka), metabolite clearance (CLm) and bioavailability (F) were evaluated as covariates of clearance (CL).