CLINICAL PHARMACOLOGY REVIEW

NDA:	21,024
Drug	Rifapentine
Trade Name	PRIFTIN
OCP & PM Reviewer	Zhixia (Grace) Yan, Ph.D.
OCP Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
PM Team Leader	Jeffry A. Florian, Ph.D.
OCP Division	DCP4
OND Division	DAIP
Sponsor	Sanofi-Aventis U.S. LLC
Submission Type; Code	Supplemental New Drug Application (new indication, which includes pediatric patients age 2 to 11 years)
Formulation; Strength(s)	150 mg Tablets
Indication	Latent Tuberculosis Infection (LTBI)
Dosage and Administration **(include and food instructions in this section)**	PRIFTIN should be administered in combination with isoniazid once-weekly for 12 weeks as directly observed therapy (DOT). Adults and children ≥ 12 years: PRIFTIN (based on weight, see table below) and isoniazid 15 mg/kg (900 mg maximum) Children 2-11 years: PRIFTIN (based on weight, see table below) and isoniazid 25 mg/kg (900 mg maximum) Take with food. Tablets may be crushed and added to semi-solid food.

Weight Range	PRIFTIN Dose	Number of PRIFTIN Tablets
10-14 kg	300 mg	2
14.1-25 kg	450 mg	3
25.1- 32 kg	600 mg	4
32.1-50 kg	750 mg	5
> 50 kg	900 mg	6

1. EXECUTIVE SUMMARY

Priftin® (Rifapentine; RPT) is currently approved in the United States (US) in adults and adolescents (≥12 years of age) for the treatment of pulmonary tuberculosis (TB) caused by *Mycobacterium tuberculosis*. The treatment regimen for this indication is 600 mg (4 × 150 mg tablets) twice weekly for two months (Initial Phase) as directly observed therapy (DOT) in combination with other anti-tuberculosis agents and 600 mg once weekly for 4 months (Continuation Phase) as DOT with isoniazid (INH) or another appropriate anti-tuberculosis agent. This supplemental New Drug Application (sNDA) submission is intended to support the addition of a new indication, treatment of latent tuberculosis infection (LTBI) in adults and children ≥2 years, to the Priftin® US labeling. Priftin® should be administered in combination with isoniazid once-weekly for 12 weeks as DOT (3RPT/INH; denotes a 3-month [12-week] treatment duration of weekly RPT and INH).

Adults and children ≥ 12 years: Priftin® (based on weight, **Table 1-1**) and isoniazid 15 mg/kg (900 mg maximum).

Children 2-11 years: Priftin® (based on weight, **Table 1-1**) and isoniazid 25 mg/kg (900 mg maximum)

Table 1-1. Weight-Based Priftin® Dose

Weight Range	PRIFTIN Dose	Number of PRIFTIN Tablets (150 mg)
10-14 kg	300 mg	2
14.1-25 kg	450 mg	3
25.1- 32 kg	600 mg	4
32.1-50 kg	750 mg	5
> 50 kg	900 mg	6

For LTBI, the maximum recommended dose of Priftin® is 900 mg once-weekly for 12 weeks. Priftin® should be taken with food. Priftin® tablets may be crushed and added to semi-solid food for patients who cannot take whole tablets.

The main component of the development program for the 3RPT/INH regimen in the treatment of LTBI is Study TBTC-S26, a clinical study sponsored and carried out by CDC's Tuberculosis Trials Consortium (TBTC) in which the effectiveness and safety of 3RPT/INH, a 12-week regimen as DOT was compared with a 9-month regimen of daily self-administered INH (9INH) in patients at high risk for developing TB disease. Also included in this sNDA submission are 2 sub-studies in which enrollment was extended beyond the end of the TBTC-S26 main study to

continue recruiting additional children ≥2 years of age (TBTC-S26 pediatric substudy) and HIV-infected patients not taking antiretroviral therapy (TBTC-S26 HIV substudy) and a nested PK substudy to evaluate the appropriateness of a weight-based dose algorithm in children (2 to 11 years old).

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed the efficacy supplement for NDA 21,024 for the treatment of latent tuberculosis infection in adults and pediatric patients, and it is acceptable from a clinical pharmacology perspective. We recommend approval of this NDA supplement.

1.2 Phase 4 Commitments/Requirements

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The biopharmaceutics profile of rifapentine is well established. No new biopharmaceutics studies were conducted in support of this submission. The rifapentine formulation used in all LTBI clinical trials is the currently marketed US formulation (150 mg tablets). Rifapentine is hydrolyzed by an esterase enzyme to form a microbiologically active 25-desacetyl rifapentine. Rifapentine and 25-desacetyl rifapentine account for 99% of the total radioactivity in plasma. Based upon relative in vitro activities and $AUC_{(0-\infty)}$ values, rifapentine and 25-desacetyl rifapentine contribute approximately 62% and 38% to the clinical activities against *M. tuberculosis*, respectively.

Pharmacokinetics in healthy subjects
The PK parameters of rifapentine and 25-desacetyl rifapentine following single-dose oral administration of 900 mg rifapentine in combination with 900 mg isoniazid (proposed maximum clinical dose) in fed conditions are summarized in **Table 1.3-1**. No substantial changes in PK of rifapentine, 25-desacetyl rifapentine, or isoniazid were observed when rifapentine and isoniazid were co-administered compared to when rifapentine or isoniazid was administered alone. Administration of rifapentine with a low fat, high carbohydrate breakfast led to a 40-50% increase in exposures of rifapentine and 25-desacetyl rifapentine.

Table 1.3-1. Mean±SD Pharmacokinetic Parameters of Rifapentine and 25-Desacetyl Rifapentine in Healthy Volunteers When Co-administered with Isoniazid Under Fed Conditions (N=16).

Parameter	Rifapentine	25-desacetyl Rifapentine
C_{max} (µg/mL)	25.8± 5.83	13.3 ± 4.83
AUC (µg*h/mL)	817 ± 128	601 ± 187
$T_{1/2}$(h)	16.6 ± 5.02	17.5 ± 7.42
T_{max} (h)*	8 (3-10)	24 (10-36)
Cl/F (L/h)	1.13 ± 0.174	NA**

*Median (Min-Max)
**Not Applicable

Pharmacokinetics in LTBI patients
A total of 80 children and 77 adults were enrolled in TBTC S26 PK Substudy. The mean rifapentine doses based on mg/kg were higher in children than in adults (23.2 versus 11.0 mg/kg). Overall, the resulting rifapentine geometric mean AUC was 31% higher in children compared to adults (720 versus 551 μg*h/mL). The weight-based dosing algorithm used in TBTC Study 26 achieved 30-60% higher rifapentine exposure in all children, except the 10-14 kg group, compared to adults. The 10.0-14.0 kg weight band was comprised of 13 children (mostly aged 2-4 years), all of whom received crushed tablets and presented with slightly lower rifapentine exposure than adults (504 versus 551 μg*h/mL). Of the 80 children, 55 (69%) could not swallow tablets and were administered crushed rifapentine tablets. The geometric mean AUC in children administered crushed rifapentine tablets was lower than that observed in children administered whole tablets (656 versus 884 μg*h/mL), but still higher compared to adults. Comparisons within pediatric weight bands between pediatrics administered crushed and whole rifapentine tablets demonstrated consistently 26% lower rifapentine exposures in pediatrics administered crushed rifapentine tablets. This observation indicates that the difference in exposures between crushed and whole rifapentine tablets is not an age-dependent phenomenon.

Efficacy and safety in LTBI patients
No pediatric patients on the 3RPT/INH arm in Study 26 developed TB disease over the 33-month follow-up period (primary clinical outcome). No serious AEs were reported in any patients who participated in the PK substudy. The frequency of treatment-related AEs in Study 26 was similar for children enrolled in and not enrolled in the PK substudy (1.3% vs. 4.0%, respectively; p=0.421).

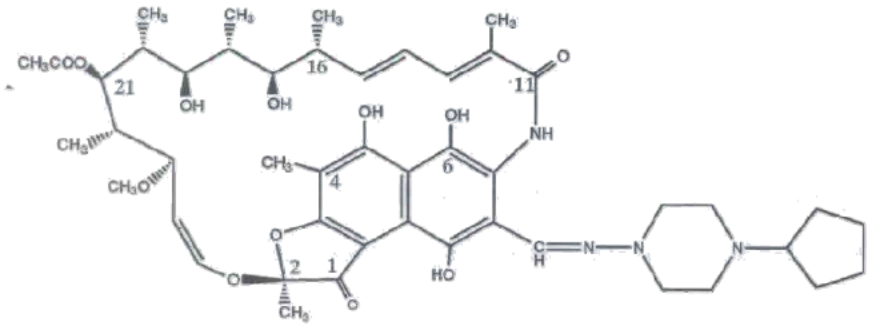
2. QUESTION-BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Priftin® (rifapentine) is an oral antimycobacterial agent derived from rifamycin. It differs from rifampin by (b) (4) (**Figure 2.1.1-1**). Priftin is supplied as 150 mg round normal convex dark-pink film-coated tablets debossed "Priftin" on top and "150" on the bottom.

Figure 2.1.1-1. Chemical Structures of Rifapentine ($C_{47}H_{64}N_4O_{12}$; MW= 877.04)



2.1.2 What are the proposed mechanism(s) of action and therapeutic indications(s)?

As a member of the rifamycin class, rifapentine abrogates transcription elongation by inhibiting the bacterial DNA dependent RNA polymerase (RNAP) through high affinity binding to the β-subunit of RNAP in susceptible strains of *M. tuberculosis* but not in mammalian cells.

Priftin® is approved in adults and adolescents ≥ 12 years of age for the treatment of pulmonary tuberculosis (TB) caused by *M. tuberculosis* in combination with one or more anti-tuberculosis drugs. The Sponsor is seeking a new indication for Priftin® in combination with INH for the treatment of latent tuberculosis infection (LTBI) caused by *M. tuberculosis* in patients at high risk of progression to TB disease, (b) (4) The Sponsor also proposes to reduce the age cutoff of the target patient population to 2 years for this new indication only.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dosage regime of Priftin® for the LTBI indication is shown as follows:

Priftin® should be administered in combination with isoniazid with food once-weekly for 12 weeks as DOT. Tablets may be crushed and added to semi-solid food.

Adults and children ≥ 12 years: Priftin® (based on weight, **Table 2.1.3-1**) and isoniazid 15 mg/kg (900 mg maximum)

Children 2-11 years: Priftin® (based on weight, **Table 2.1.3-1**) and isoniazid 25 mg/kg (900 mg maximum)

Table 2.1.3-1. Weight-Based Priftin® Dose

Weight Range	PRIFTIN Dose	Number of PRIFTIN Tablets (150 mg)
10-14 kg	300 mg	2
14.1-25 kg	450 mg	3
25.1- 32 kg	600 mg	4
32.1-50 kg	750 mg	5
> 50 kg	900 mg	6

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Two drug-drug interaction studies (INT12099 in healthy subjects and INT12291 in HIV-infected patients), one PK substudy nested in the main TBTC Study 26 comparing pharmacokinetic (PK) in pediatric and adult patients with LTBI (TBTC-S26 PK substudy), as well as in vitro studies were performed to characterize PK of rifapentine in support of the proposed indication of a combined 3RPT/INH regimen for the treatment of LTBI in patients at high risk for developing TB disease. Data from TBTC-S26 PK substudy were used along with previously published two Phase 1 clinical studies (children, adolescents) and one Phase 1/2 clinical study (TBTC Study 25) for development of population PK models.

Efficacy and safety of the 3RPT/INH regimen in the treatment of LTBI was assessed in one pivotal Phase 3 trial (TBTC-S26). Also included in this sNDA submission are 2 substudies in which enrollment was extended beyond the end of the TBTC-S26 main study to continue recruiting additional children ≥2 years of age (TBTC-S26 pediatric substudy) and HIV-infected patients not taking antiretroviral therapy (TBTC-S26 HIV substudy) (**Table 2.2.1-1**).

Table 2.2.1-1 Overview of Clinical Trials for the 3RPT/INH Regimen

Study No.	Design	3RPT/INH DOT Regimen	Comparator 9INH Self-Administered Regimen	Population Size
Phase 3				
TBTC-S26 Main Study	Multicenter, prospective, randomized, open-label comparative study	RPT and INH once-weekly for 12 weeks as DOT. ≥12 years old: RPT (weight-based; 900 mg max); INH 15 mg/kg (900 mg max) 2-11 years old: RPT (weight-based; 900 mg max); INH 25 mg/kg (900 mg max)	INH: once daily for 9 months ≥12 years old: 5 mg/kg (300 mg max) 2-11 years old: 10-15 mg/kg (300 mg max)	3RPT/INH: N = 4040 9INH: N = 3759
TBTC-S26-HIV Substudy				3RPT/INH: N = 207 9INH: N = 186
TBTC-S26-Pediatric Substudy				3RPT/INH: N = 539 9INH: N = 493

2.2.2 What are the key efficacy findings?

TBTC-S26 main study

The primary endpoint was the development of active tuberculosis disease at 33 months after study enrollment, defined as culture confirmed tuberculosis in adults and culture-confirmed or clinical tuberculosis in children ≤18 years of age The primary endpoint analysis was performed in the modified intent to treat (MITT) population defined as all randomized patients excluding patients found to be contacts of drug-resistant TB disease or culture-negative source cases, and young children lacking a positive tuberculin skin test (TST) on initial and repeat testing.

TBTC-S26 main study
Tuberculosis developed in 7 of 3986 patients in the 3RPT/INH group (cumulative rate, 0.19%) versus 15 of 3745 patients in 9INH group (cumulative rate, 0.43%), for a difference of 0.24% (**Table 2.2.2-1**). Rates of treatment completion were 82.1% in the 3RPT/INH group and 69% in the 9INH group ($p<0.001$). Rates of permanent drug discontinuation due to a treatment- related adverse reaction were 4.9% in the 3RPT/INH and 3.7% in the 9INH therapy group ($p = 0.009$).

Table 2.2.2-1 Number of TB Cases and Event Rates by Treatment Arm: TBTC-S26 main study (MITT population, 33 month analysis)

Treatment Arm	# TB Cases	Cumulative TB Rate (%)	Difference in Cumulative TB Rate (%)	Upper Bound (%) of 95% Confidence Interval*
9INH	15	0.43	-0.24	0.01
3RPT/INH	7	0.19		

Note: Adapted from Module 2.5, Clinical Overview.
* *The non-inferiority margin was 0.75%.*

Pediatric substudy
The results of the analysis of development of TB disease in the pediatric population were consistent with the TBTC-S26 main study population. Three children under 18 years old developed TB disease, including a 2-year-old male (clinical TB), a 5 year-old male (clinical TB), and a 14-year-old female (culture-confirmed TB), all enrolled in the 9INH arm, resulting in cumulative TB event rates of 0.78% for the 9INH arm and 0% for the 3RPT/INH arm. The treatment completion rate in the MITT population was higher among children in the 3RPT/INH group than in children in the 9INH group: 88.1% versus 81%, respectively ($p=0.003$).

HIV substudy
In the TBTC-S26 HIV substudy at 33 months after study enrollment, TB disease developed in 6 of 193 patients in the 9INH arm and 2 of 206 patients in the 3RPT/INH arm, resulting in cumulative TB event rates of 3.50% for the 9INH arm and 1.01% for the 3RPT/INH arm. Four of the 8 HIV-infected patients who developed TB were enrolled in the main study and are also included in the analysis for the main study (2 in the 9INH arm and 2 in the 3RPT/INH arm).

2.2.3 What are the key safety findings?

TBTC-S26 main study
Seventy one (71) deaths occurred, 31/4040 (7.7%) in the 3RPT/INH group and 40/3759 (10.6%) in the 9INH group during the 33 months study period. During the treatment period, 11 deaths occurred, 4 in the 3RPT/INH group and 7 in the 9INH group. None of the reported deaths were considered related to treatment with study drugs or were attributed to tuberculosis disease. A total of 161 (4%) subjects in the 3RPT/INH arm had a rifamycin hypersensitivity reaction. 113 (3%) subjects in the 9INH group and 24 (0.6%) subjects in the 3RPT/INH group developed hepatitis. Please consult the review by the Medical officer (Dr. Hala Shamsuddin) for details regarding the safety of the 3RPH/INH therapy.

Pediatric substudy
Seven children (1.3%) in the 3RPT/INH group experienced a rifamycin hypersensitivity reaction. No children in either treatment arm developed hepatotoxicity. Adverse reactions in children 2-11 years of age and 12-17 years of age were similar.

HIV substudy
Eleven deaths occurred during the 33 months follow up period (6/207 in the 3RPT/INH group and 5/186 in the 9INH group). None of the reported deaths were considered related to treatment with study drugs or tuberculosis disease. Seven patients in the 3RPT/INH group and 8 patients in the 9INH group discontinued treatment due to treatment related adverse event. Hepatitis was the most frequent cause of discontinuation (2 in the 3RPT/INH group and 8 in the 9INH group).

2.2.4 What are the key pharmacokinetic findings?

The PK sub-study nested in the efficacy/safety TBTC S26 main study used a parallel group design in children (aged 2 to 11 years) and adults (aged ≥18 years). The objective was to determine in patients with LTBI if rifapentine exposure ($AUC_{0\text{-}inf}$) was equivalent (-20% to +25%) in children (ages 2 to 11 years) receiving weekly rifapentine weight-based dosing (**Table 2.1.3-1**) to that of adults receiving weekly rifapentine 900 mg. The study treatment was the same as the main study (3RPT/INH). In children who could not swallow whole tablets, rifapentine was administered as a suspension of crushed tablets along with INH pills (alternatively, INH could have been administered in liquid formulation) in either a soft food or liquid (e.g., a starch-based pudding was recommended; fruit-based carriers were not recommended). In this study, a single blood sample was withdrawn (24 hours after the third or subsequent once weekly 3RPT/INH dose) and a population PK model based on data obtained from 4 clinical studies (TBTC Study 25, TBTC-S26, children and adolescent study) was used to determine rifapentine AUC.

2.2.4.1 Does the evaluated pediatric dosing result in comparable pediatric rifapentine exposures to those observed in adults?

Results from this PK substudy demonstrated that rifapentine exposures were not comparable between children (ages 2 to 11 years) receiving weight-based dosing and adults receiving rifapentine 900 mg. The dosing algorithm used in TBTC Study 26 in children (aged 2 to 11 years) produced approximately 31% higher mean rifapentine AUC in Children compared to mean rifapentine AUC in adults receiving a standard 900-mg dose (720 versus 551 µg*h/mL; **Table 2.2.4.1-1**). Rifapentine AUC was 60% higher in children administered whole tablets (884 versus 551 µg*h/mL) and 19% higher in children administered crushed tablets (656 versus 551 µg*h/mL), as compared to exposures in adults (**Table 2.2.4.1-1**). The similar trend was observed with the AUC of 25-desacetyl-rifapentine in children compared to adults. Previous studies showed that rifapentine concentrations at 24 hours post-dose (C_{24}) correlated well with rifapentine AUC. The results derived from observed rifapentine C_{24} agree with those derived from AUC predicted by the population PK model (**Table 2.2.4.1-1**).

Table 2.2.4.1-1. Model Predicted AUC and Observed C_{24} of Rifapentine by Tablet Integrity

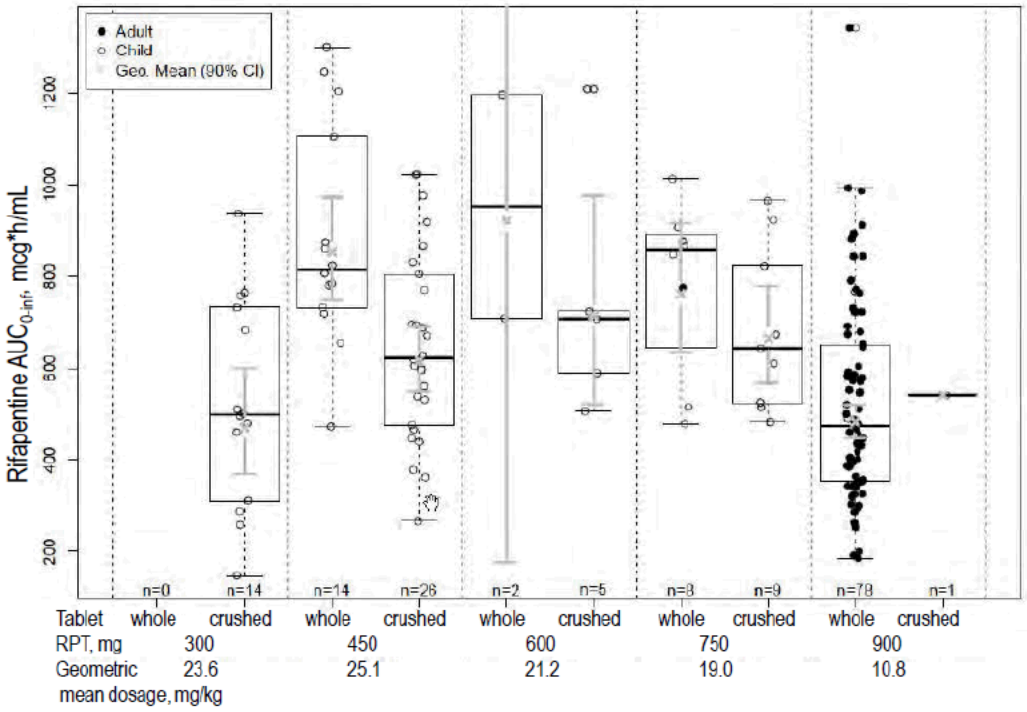
Rifapentine	Children			Adult N=77
	All children N=80	Whole Tablet N=25	Crushed Tablet N=55	
Model Predicted AUC (µg*h/mL)				
Geometric Mean	720	884	656	551
CV%	38	26	39	0.36
Geometric Mean Ratio (vs. Adults) *p*-value (vs. Adults)*	1.31 <0.0001	1.60 <0.0001	1.19 0.005 {0.0004†}	N.A.
Observed C_{24} (µg/mL)				
Geometric Mean	10.9	14.1	9.7	8.5
CV%	57	33	61	0.48
Geometric Mean Ratio (vs. Adults) *P*-value (vs. Adults)*	1.28 0.002	1.66 <0.0001	1.14 0.16 {0.001†}	N.A.

Note: AUC and C_{24} data are extracted from Sponsor's report of TBTC Study 26 PK, Table S11. Results from Reviewer's analysis on C_{24} agree with those from Sponsor's analysis (See Pharmacometric Review for details in Appendix 4.2).

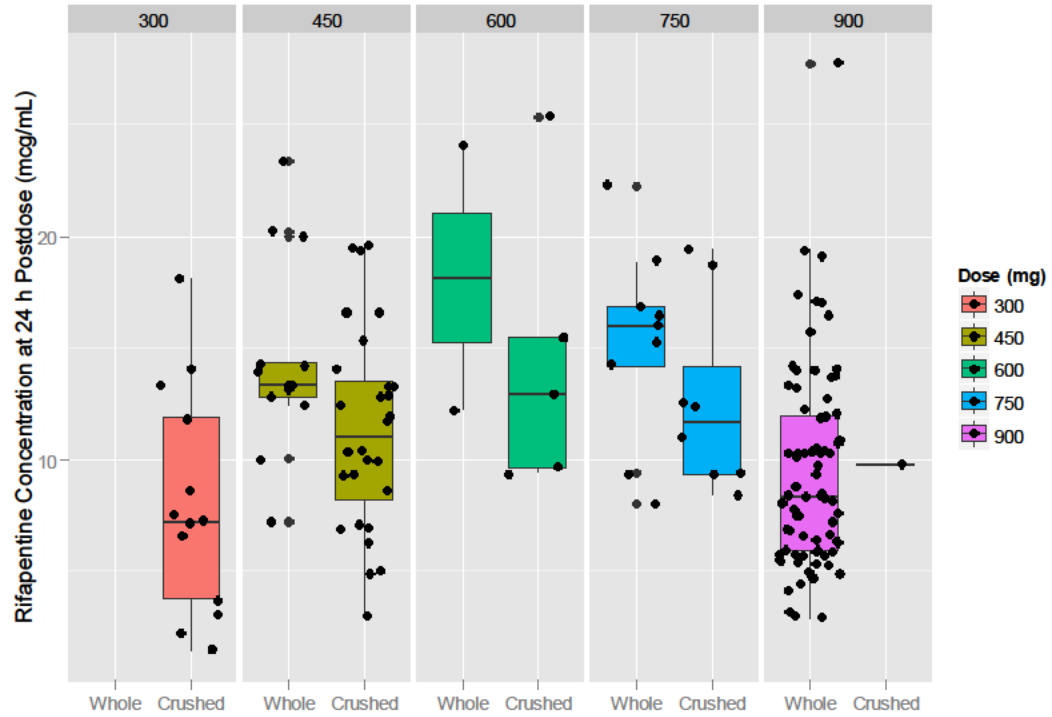
**P-value based on t-test on $\log_e$ transformed data in comparison of all children vs. adults and by Fisher's LSD in each children group (whole or crushed tablet) vs. adults. † P-value by Fisher's LSD for comparison between children administered whole vs. crushed rifapentine tablets.*

The weight-based dosing algorithm used in TBTC Study 26 achieved 30-60% higher rifapentine exposure (both predicated AUC and observed C_{24}) in all children, except the 10-14 kg group, compared to adults (**Figure 2.2.4.1-1** and **Table 2.2.4.1-2**). The 10.0-14.0 kg weight band was comprised of 13 children (mostly aged 2-4 years), all of whom received crushed tablets and presented with slightly lower rifapentine exposure than adults (**Figure 2.2.4.1-1** and **Table 2.2.4.1-2**). Comparisons within pediatric weight bands between pediatrics administered crushed and whole rifapentine tablets demonstrated consistently 26% lower rifapentine exposures in the pediatric patients administered crushed rifapentine tablets (See **Table 3.3.5-1** in the Pharmacometric Review in Appendix 4.2 for details). One possible explanation is that children may not consume the entire quantity of the crushed tablet given with soft food or liquid. Population PK analysis also showed that food increased rifapentine exposure (both predicated AUC and observed C_{24}) in both children (by 25-30%; $p>0.05$) and adults (by 40%; $p<0.0001$) (**Table 2.2.4.1-3**). Therefore, children in the lowest weight band (10-14 kg) who take crushed tablets with food would be expected to achieve comparable exposure to adults.

Figure 2.2.4.1-1. Model Predicted Rifapentine AUC (Top Panel; Sponsor's Analysis) and Observed C_{24} (Bottom Panel; Reviewer's Analysis) by Rifapentine Dose (Weight Band) and Tablet Integrity (Crushed or Whole)



Note: Adapted from Sponsor's report of TBTC Study 26 PK, Figure S2.



Note: See Pharmacometric Review in Appendix 4.2 for details.

Table 2.2.4.1-2. Model Predicted Rifapentine AUC (Top Panel; Sponsor's Analysis) and Observed C_{24} (Bottom Panel; Reviewer's Analysis) by Rifapentine Dose (Weight Band) and Tablet Integrity (Crushed or Whole)

Weight Band (kg)	Age Group	RPT Dose (mg)	N	Tablet Integrity	Geometric Mean of RPT mg/kg[a]	RPT AUC (mcg*h/mL)						
						Geometric Mean RPT AUC (90% CI)	CV	Min	25th Percentile	Median	75th Percentile	Max
10.0-14.0	Child	300	13	Crushed	23.6	504 (399-637)	0.5	184.7	375.7	489.9	706.5	989.3
14.1-25.0	Child	450	26	Crushed	25.3	744 (684-810)	0.32	365.7	584.4	765.9	968.1	1301.4
		450	13	Whole								
25.1-32.0	Child	600	4	Crushed	21.3	762 (558-1041)	0.34	545	637.4	746.5	765.5	1297
		600	1	Whole								
32.1-50.0	Adult	750	1	Whole	18.7	813 (721-916)	0.28	539.5	615.6	883.9	1022.4	1184.2
	Child	750	8	Crushed								
		750	7	Whole								
>50	Adult	900	76	Whole	10.8	551 (517-588)	0.35	263.6	440.1	554.6	733.5	1300.7
	Child	900	1	Crushed								
		900	2	Whole								

Note: Adapted from Sponsor's report of TBTC Study 26 PK, Table S13. Table based on those participants who received the correct rifapentine dose for their weight band. Children that did not receive the correct rifapentine dose based on their weight band were removed. These include: 1 child in weight band 10.0-14.0 kg who received rifapentine 450 mg; 1 child in weight band 14.1-25.0 kg who received rifapentine 600 mg; 2 children in weight band 25.1-32.0 kg, where 1 received rifapentine 450 mg and the other received rifapentine 750 mg; and 1 child in weight band 32.1-50.0 kg who received rifapentine 600 mg.

[a]*Geometric Mean RPT mg/kg by RPT dose.*

Weight Band (kg)	Age Group	RPT Dose (mg)	N	Tablet Integrity	Geometric Mean of RPT mg/kg	RPT C_{24} (µg/mL)						
						Geometric Mean	CV	Min	25th Percentile	Median	75th Percentile	Max
10.0-14.0	Child	300	13	Crushed	23.6	6.4	0.88	1.4	3.7	7.2	11.9	18.1
14.1-25.0	Child	450	26	Crushed	25.3	11.3	0.47	3.0	9.3	12.8	14.2	23.4
			13	Whole								
25.1-32.0	Child	600	3	Crushed	21.3	14.0	0.43	9.6	11.6	12.6	16.1	25.3
			1	Whole								
32.1-50.0	Adult	750	1	Whole	18.7	13.0	0.31	8.0	8.3	13.4	16.6	19.4
	Child		8	Crushed								
			7	Whole								
>50	Adult	900	76	Whole	10.8	8.5	0.48	2.9	4.4	8.4	11.9	27.7
	Child		1	Crushed								
			2	Whole								

Note: See Pharmacometric Review in Appendix 4.2 for details.

Table 2.2.4.1-3. Comparisons of Model Predicted Rifapentine AUC (Top Panel; Sponsor's Analysis) and Observed C_{24} (Bottom Panel; Reviewer's Analysis) in Both Children and Adults When Administered With and Without Food

Population	N	Geometric Mean RPT AUC (mcg*h/mL)	CV	Min	Max	90% CI	*P*-value*
Child with Food	70	740.3	0.34	283.0	1333.7	(693.1, 790.8)	0.23
Child with no Food	10	590.2	0.59	184.7	1095.5	(430.5, 809.0)	
Adult with Food	53	613.8	0.33	273.7	1300.7	(570.2, 660.8)	<0.0001
Adult with no Food	24	434.3	0.29	263.6	847.2	(393.3, 479.6)	

Note: Adapted from Sponsor's report of TBTC Study 26 PK, Table S18.
**P-value based on t-test using lognormal transformation.*

Population	N	Geometric Mean RPT C_{24} (µg/mL)	CV	Min	Max	90% CI	*P*-value
Child with Food	70	11.3	0.51	2.2	25.3	(11.0, 11.6)	0.33
Child without Food	10	8.7	0.93	1.4	19.5	(7.4, 9.9)	
Adult with Food	53	9.5	0.47	2.9	27.7	(9.1, 9.8)	0.0016
Adult without Food	24	6.7	0.42	3.0	17.0	(6.2, 7.3)	

Note: See Pharmacometric Review in Appendix 4.2 for details.

2.2.4.2 Are the proposed pediatric dosing recommendations supported by observations from TBTC Study 26?

The proposed weight-based dosing regimen was used in pediatric patients (ages 2-11 years) enrolled in the TBTC Study 26. Despite the generally increased exposure observed in children 2 to 11 years of age in this PK substudy, no increase in the incidence or severity of adverse events (AEs) was observed and no serious AEs were reported in any patients who participated in the PK substudy. The frequency of treatment-related AEs in Study 26 was similar for children enrolled in and not enrolled in the PK substudy (1.3% vs. 4.0%, respectively; p=0.421). In addition, although lower rifapentine exposure, compared to adults, was observed in younger children (mostly aged 2-4 years in the 10-14 weight band) who received crushed tablets, an decrease in efficacy was not observed as no pediatric patients on the 3RPT/INH arm in Study 26 developed TB disease over the 33-month follow-up period (primary clinical outcome). Therefore, the proposed pediatric dosing recommendations are supported by observations from TBTC Study 26.

2.2.4.3 How do the PK parameters change with time following chronic dosing?

Half-lives of rifapentine and 25-desacetyl rifapentine (active metabolite) range from 16-17 hours (**Table 1.3-1**); no plasma accumulation of rifapentine and 25-desacetyl rifapentine is expected after once weekly administration of rifapentine. Population PK analysis showed no significant auto-induction effect on rifapentine PK with once-weekly administration of rifapentine.

2.2.4.4 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Population PK analysis showed that the inter-patient variability was 40% for rifapentine oral clearance and 47% for volume of distribution. The inter-patient variability was 64% for metabolite clearance. In healthy subjects, after single administration of 900 mg in fasted conditions, within-subject variability of rifapentine C_{max} and AUC were moderate, 33% and 36% respectively (Study INT12099). Inter-subjects variability (CV %) for rifapentine C_{max} and AUC ranged from 36% to 44% in fasting conditions and decreased to 16% -23% in fed conditions.

Intrinsic sources of variability in healthy subjects have been evaluated in specific studies submitted in the original application. For the proposed new LTBI treatment regimen in this sNDA, extrinsic sources of variability that were investigated included the co-administration with isoniazid and the food effect (Study INT12099). In patients, intrinsic sources of PK variability included age and body weight; whereas, extrinsic source of variability evaluated were food and tablet integrity (see Pharmacometric Review in Appendix 4.2 for details).

2.3 Intrinsic Factors

The effect of age and body weight on rifapentine PK in pediatric patients was evaluated and described in section 2.2. Please see the same section for the recommendation of dosing regimen as a function of body weight in pediatric patients. The influence of other intrinsic factors on rifapentine PK was characterized and described in the currently approved Priftin® US labeling.

2.4 Extrinsic Factors

2.4.1 Is there an in vitro basis to suspect *in vivo* drug-drug interactions?

Rifapentine is an inducer of CYP3A4 and CYP2C8/9 [redacted]

2.4.2 Does the label specify co-administration of another drug, and if so, has the interaction potential between these drugs been evaluated?

This sNDA submission is intended to support the rifapentine and isoniazid combination therapy for the treatment of LTBI in adults and children ≥2 years. Study INT12099 was conducted to evaluate the drug-drug interactions between a single oral dose of 900 mg rifapentine and a single oral dose of 900 mg isoniazid in 17 healthy subjects. Co-administration of rifapentine and isoniazid, in fasted condition, did not result in substantial change in plasma exposures of rifapentine, 25-desacetyl rifapentine, and isoniazid compared to administration of rifapentine or isoniazid alone (**Table 2.4.2-1**).

Table 2.4.2-1. Treatment Ratio Estimates and 90% Confidence Interval for PK parameters of Rifapentine, 25-Desacetyl Rifapentine, and Isoniazid (Rifapentine+Isoniazid versus Rifapentine or Isoniazid Administered Alone in Fasting Conditions)

PK Parameters	Point Estimates (90% CI)		
	Rifapentine	25-Desacetyl Rifapentine	Isoniazid
C_{max}	0.94 (0.76 to 1.17)	0.91 (0.72 to 1.15)	0.94 (0.81 to 1.10)
AUC	0.91 (0.72 to 1.15)	0.89 (0.68 to 1.15)	0.97 (0.92 to 1.03)

2.4.3 What other co-medications are likely to be administered to the target patient population?

Tuberculosis is a major cause of morbidity in HIV/AIDS patients. It was, therefore, relevant to evaluate the drug-drug interaction of rifapentine with one of the first-line anti-retroviral drugs. Study INT12291 was designed to evaluate the effect of once-weekly administration of 900 mg rifapentine under fed state on steady state PK parameters of efavirenz 600 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg given as a fixed dose combination (Atripla™) and to evaluate the safety and tolerability of concomitant administration of rifapentine and Atripla in HIV-infected subjects. Twelve HIV-infected, patients with a CD4 count ≥350 cells/mm^3 and viral load below the limit of quantification, receiving Atripla as background therapy, were

enrolled in an open-label, single sequence, 2-period, non-randomized study. This study did not evaluate the effect of Atripla on rifapentine PK.

Overall, once-weekly co-administration of 900 mg rifapentine with Atripla in HIV- infected patients did not result in any substantial change in steady state exposures of efavirenz, emtricitabine, and tenofovir (**Table 2.4.3-1**). A 15% decrease in efavirenz C_{min} and AUC and a 13% decrease in tenofovir C_{min} were observed with repeated weekly doses of PRIFTIN (**Table 2.4.3-1**). No clinically significant change in CD4 cell counts or viral loads were noted. No dose adjustment is recommended for Atripla when co-administered with once-weekly dosing of rifapentine.

Table 2.4.3-1. Treatment Ratio Estimates (with versus without Repeated Once-Weekly Rifapentine 900 mg) with 90% Confidence Intervals for Efavirenz, Emtricitabine and Tenofovir PK Parameters

PK Parameters	Point Estimates (90% CI)		
	Efavirenz	**Emtricitabine**	**Tenofovir**
C_{max}	0.92 (0.82 -1.03)	0.95 (0.81- 1.10)	1.00 (0.82 -1.22)
C_{min}	0.85 (0.79- 0.93)	0.97 (0.90- 1.05)	0.87(0.73 - 1.05)
AUC	0.86 (0.79- 0.93)	0.93 (0.89- 0.98)	0.91(0.85 -0.98)

2.5 General Biopharmaceutics

2.5.1 How is the proposed to-be-marketed formulation of the drug linked to the clinically used formulation?

The rifapentine formulation used in all LTBI clinical trials is the currently marketed US formulation (150 mg tablets).

2.5.2 What is the effect of food on the bioavailability of the drug when administered as drug product?

The effect of food on rifapentine bioavailability has been previously characterized and is described in the currently approved Priftin® US labeling, "the administration of rifapentine with a high fat meal (850 total calories: 33 g protein, 55 g fat and 58 g carbohydrate) increased $AUC_{0-\infty}$ and C_{max} by 43% and 44%, respectively over that observed when administered under fasting conditions". Thus, rifapentine taken with food is recommended in the currently approved Priftin® US labeling.

Under this sNDA, a Phase 1 study was conducted to assess the effect of a low fat, high carbohydrate breakfast on PK of rifapentine and isoniazid following single dose administration. Results showed that the administration of rifapentine and isoniazid (900 mg single dose) with a low fat, high carbohydrate breakfast, led to a 40-50% increase in rifapentine and 25-desacetyl rifapentine C_{max} and AUC. In contrast, the ingestion of the same meal decreased isoniazid C_{max}

and AUC by 46% and of 23%, respectively. The clinical significance of this magnitude of decrease in isoniazid exposure when taken with food is unknown. [redacted] food intake with administration of isoniazid is stated in the currently approved isoniazid US labeling.

(b) (4)

2.6 Analytical Section

Overall, the validation and performance of bioanalytical assays used for determination of rifapentine and 25-desacetyl rifapentine are deemed acceptable by the Clinical Pharmacology reviewer. An assessment of specific assay characteristics follows.

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Concentrations of rifapentine and 25-desacetyl rifapentine in plasma were quantified by validated LC-MS/MS and LC-UV assays.

2.6.2 Which metabolites have been selected for analysis and why?

In addition to rifapentine, the concentrations of the microbiologically active metabolite, 25-desacetyl rifapentine, was also measured in plasma. Rifapentine and 25-desacetyl rifapentine accounted for 99% of the total radioactivity in plasma.

2.6.3 What bioanalytical methods are used to assess concentrations?

Validated LC-MS/MS and LC-UV assays were used for quantification of rifapentine and 25-desacetyl rifapentine in plasma (**Table 2.6.3-1**).

Table 2.6.3-1 Summary of Analytical Methods for Quantification of Rifapentine and 25-Desacetyl Rifapentine in Plasma

Clinical Studies	Analytes	Method	Calibration Range (µg/mL)	Quality Control (µg/mL)	Precision CV%		Accuracy %
					Within Run	Between Run	
DDI with INH (INT 12099)	Rifapentine	LC-MS/MS	0.05-10	0.15, 5.00, 8.00	2.2-4.8	1.6-11.7	Within ±12.9
	25-desacetyl Rifapentine				2.3-4.4	2.7-8.5	Within ±8.9
DDI with Atripla™ (INT 12099)	Rifapentine	LC-MS/MS	1.00-100	3, 50, 80	4.3-8.4	0.7-10.1	Within ±6
	25-desacetyl Rifapentine				3.7-10.9	0.0-9.7	Within ±7.7
TBTC 26 PK Sub-study	Rifapentine	LC-UV	0.5-50	3, 8, 24	3.8-11.2	5.3-13.2	Within ±8.3
	25-desacetyl Rifapentine				6.2-8.2	9.8-18.3	Within ±13.9

Adapted from 2.7.2 Summary of Clinical Pharmacology studies

2.6.3.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

See **Tables 2.6.3-1**.A linear least-squares regression ($y = mx + b$, where x is the concentration and y is the peak area ratio) was applied for all standard curves with a weighting factor of $1/\text{concentration}^2$ ($1/y^2$).

2.6.3.2 What are the accuracy, precision, and selectivity at these limits?

See **Tables 2.6.3-1**.

2.6.3.3 What is the QC sample plan?

See **Tables 2.6.3-1**.

2.6.3.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, and sample-handling)?

Rifapentine and 25-desacetyl rifapentine were stable in human plasma at room temperature and +4°C for at least 24 hours and following at least three freeze/thaw cycles (-20°C and -80°C). In addition, rifapentine was stable at approximately -20°C and -80°C for at least 110 days. 25-desacetyl rifapentine was stable at least 44 days at -20°C and -80°C. Rifapentine and 25-desacetyl rifapentine were stable in blood at +4°C for at least 2 hours and 4 hours, respectively.

3. DETAILED LABELING RECOMMENDATIONS

The following proposed package insert has been marked by revisions made by the Reviewer, indicated with ~~red strikethrough font~~ for deleted text and underlined blue font for inserted text. Affected sections include **Highlights, Warnings and Precautions (5), Drug Interactions (7), Use in Specific Populations (8)**, and **Clinical Pharmacology (12)**.

39 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

APPENDICES

4.1 Individual Clinical Pharmacology Study Report Reviews

STUDY NO.: TBTC

TBTC Study 26 PK: Rifapentine Pharmacokinetics in Children Receiving Once Weekly Rifapentine and Isoniazid for the Treatment of Latent Tuberculosis Infection

Date(s): 04 May 2006 to 13 April 2011
Sponsor: SANOFI AVENTIS US LLC
Clinical Site: Eight centers in the United States participated in the pharmacokinetic substudy
Analytical Site: 39 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

OBJECTIVE(S):

Primary

- Determine in patients with latent TB infection (LTBI) if rifapentine (RPT) exposure was equivalent (-20% to +25%) between children (ages 2 to 11 years) receiving weight-based dosing and adults receiving RPT 900 mg.

Secondary

- Correlate estimated RPT exposure with toxicity in young children receiving RPT and isoniazid (INH) for LTBI;
- Validate the accuracy of estimated RPT exposure with pediatric RPT dose based on weight (using a dosing algorithm developed from PK studies in children and adults);
- Determine estimated drug bioavailability in pediatric patients (ages 2 to 11 years) given higher mg/kg doses of RPT;
- Determine the effects of polymorphisms of transporter genes on RPT PK parameters in adults; and
- Determine the frequency of lower antitubercular drug concentrations in adults with acetylator status determined by N-acetyltransferase genotypes.

METHODS

Study Design: This study was a nested PK substudy of TBTC Study 26 (main study) and used a parallel-group design with adults (aged ≥18 years) serving as control cases for children (aged 2 to 11 years). Eligible children enrolled in Study 26 and randomized to receive weekly RPT plus INH for 3 months (3RPT/INH) were candidates for the PK substudy at TBTC. In this nested PK substudy, adults (aged ≥18 years) enrolled in Study 26 randomized to receive 3RPT/INH served to allow comparison of adult RPT PK parameters with that of children (aged 2 to 11 years). With the enrollment of a child, an adult control was eligible for enrollment. Preferences to be followed for substudy participation were: 1) child's biological parent of the same sex; 2) child's biological parent; or 3) next eligible adult of the same sex at the same TBTC site. This PK substudy involved collection of a single PK sample 24 hours after the third or subsequent once-weekly 3RPT/INH dose.

Study Treatment

3RPT/INH Treatment Arm

Patients 2 to 11 years of age received INH 25 mg/kg (rounded up to nearest 50 or 100 mg; 900 mg maximum) once-weekly, orally (PO), by DOT for 12 doses (3 months). Directly observed therapy (DOT) was defined as a healthcare worker observing ingestion of each dose of study drug.

In combination with the INH, RPT was administered once weekly, PO, by DOT for 12 doses (3 months) based on the weight ranges in **Table 1**. The dosing algorithm was based on a regression model derived from observed RPT exposures in an initial pediatric study and simulations that used the relation between age and dose-corrected total body exposure in children and adults.

Table 1. Pediatric Rifapentine Doses

Weight Range	Rifapentine Dose	
10.0-14.0 kg	300 mg	21.4-30.0 mg/kg
14.1-25.0 kg	450 mg	18.0-31.9 mg/kg
25.1-32.0 kg	600 mg	18.8-23.9 mg/kg
32.1-50.0 kg	750 mg	15.0-23.4 mg/kg
>50.0 kg	900 mg	≤18.0 mg/kg

NOTE: Children who weighed <10.0 kg were excluded from the study.

Children who could not swallow tablets/pills whole were administered a suspension of crushed RPT tablets along with INH pills (alternatively, INH could have been administered in liquid form) in either a soft food or liquid (e.g., a starch-based pudding was recommended; fruit-based carriers were not recommended). The entire slurry was to be immediately consumed, and the cup was to be rinsed with 15 mL of water and this rinse was also to be administered to ensure that the complete dose was administered. Other foods consumed within 2 hours of drug administration were to have been documented.

Adults >50 kg received 900 mg INH and RPT 900 mg once weekly, PO, by DOT for 12 doses (3 months).

Inclusion Criteria: Children between the ages of 2 to 11 years and adults aged 18 years or older for whom informed consent was obtained (for children between the ages of 7 and 11 years informed consent by a guardian as well as an assent were obtained) who were enrolled in TBTC Study 26 and randomized to receive 3RPT/INH were eligible for inclusion in the Study 26 PK substudy. In addition, patients had to be willing to undergo a blood phlebotomy 24 hours following dosing of INH and RPT after receiving at least 3 once-weekly doses of RPT/INH.

PK Sample Collection: A blood sample (2 mL) was obtained from both children and adults for PK analysis of RPT concentrations 24 hours after the third or subsequent once-weekly RPT/INH dose. Blood samples should have been obtained as close to the 24-hour time point as possible after drug administration, but samples obtained within 60 minutes of that point (i.e., 23 to 25

hours after drug administration) were acceptable. Adults were required to abstain from alcohol for 24 hours before RPT administration and during the 24-hour PK sampling period.

Analytical Methods: Plasma RPT and 25-desacetyl-RPT concentrations were determined using a validated high-performance liquid chromatography (HPLC) assay. 39 Pages of was used as an internal standard. Calibration standard responses were linear over the range of 39 Pages of µg/mL, using a $1/Y^2$ weighted linear regression (**Table 2**).

Table2. Bioanalytical results of TR-701, TR-700, and linezolid in plasma /urine

Criterion	RPT	25-desacetyl-RPT	**Comments**
Calibration Range	0.5-50 µg/mL	0.5-50 µg/mL	Satisfactory
LLOQ	0.1 µg/mL	0.1 µg/mL	Satisfactory
Linearity, mean R^2	>0.9949	>0.9803	Satisfactory
Overall Precision	3.49-10.65 %		Satisfactory
Recovery from Plasma	95 %		Satisfactory
Quality Control	3, 8, 24 µg/mL	3, 8, 24 µg/mL	Satisfactory
Intra-batch Accuracy	93.34-97.08 %	86.27-104.50 %.	Satisfactory
Intra-batch Variability	3.76-11.16 %	6.17-8.24 %	Satisfactory
Inter-batch Accuracy	91.69-96.36 %	100.19-113.93 %	Satisfactory
Inter-batch Variability	5.33-13.15 %	9.77-18.33 %	Satisfactory
Stability	Stability at -80 ºC was at least one year; After stored at 4 and 20 ºC for 24 hours, accuracy of the expected standard (1 µg/mL) was 83.2-96.8 %		Satisfactory

Pharmacokinetic Analysis: Initially it was planned to (b) (4) . However in this study, the RPT PK parameters were estimated using a nonlinear, mixed effect (NLME) regression population PK model (NONMEM, version 7 software). This model was also used to ascertain if C_{24} measured in the present study was sufficient to accurately estimate the exposure.

This model was developed based on data pooled from 4 studies of RPT (**Table 3**). PK profiles from a total of 1634 RPT and 25-desacetyl-RPT concentration levels from 227 subjects were used in this analysis.

Table 3. Summary of Studies Included in the Population PK Analysis

Study	Phase	n[a]	Population	Treatment	Rifapentine Dose
TBTC 25[7,8]	1/2	35	Adult Patients with TB	RPT + INH	600 mg, 900 mg, 1200 mg weekly
TBTC 26[1]	3	157	Children and adults with LTBI	RPT + INH	300 - 900 mg weekly
Children[3]	1	23	Children without TB	RPT	150 mg, 300 mg single dose
Adolescents[9]	1	12	Healthy adolescents	RPT	450 mg, 600 mg single dose

Abbreviations: TBTC=Tuberculosis Trials Consortium; TB=tuberculosis; RPT=rifapentine; INH=isoniazid; n=number; LTBI=latent tuberculosis infection; PK=pharmacokinetic

a Number of subjects receiving RPT included in the population PK analysis.

Models were sequentially developed for children and adults, and the models were merged for joint analysis of all available data. For both children and adults, a model for RPT was developed, metabolite data were added, and the RPT and metabolite data were analyzed simultaneously. After separate models were established for children and adults, the 2 models were combined. Similarities and differences between PK parameters in children and adults were evaluated.

For children and adolescents, a model was developed using RPT PK data sets with intensive sampling. Using this model, the RPT PK profiles were predicted with sparse data from children in Study 26 using a visual predictive check. Rich and sparse data from children were joined, the model was refined, and all parameters were re-estimated. The same procedure was performed for adult data using intensive sampling data from TBTC Study 25 to establish an initial model structure.

Once the population PK model was developed, $AUC_{0\text{-}inf}$ and CL/F for RPT and $AUC_{0\text{-}inf}$ for 25-desacetyl-RPT were estimated from the model and subsequent final analyses used the modeled values rather than C_{24}.

The individual parameters were assumed to be log-normally distributed and a combined error model was employed to describe residual variability. The model building process was guided by the likelihood ratio test, diagnostic plots, and internal model validation techniques, including visual and numerical predictive checks. The final model included covariates of patient weight, age, RPT dose (mg), tablet integrity (crushed or whole tablet), and food ingestion within 2 hours of study drug administration.

Reviewer Comment: Please see "Pharmacometric Review" for assessment of appropriateness of estimation of rifapentine AUC by the population PK model.

Statistical Analysis: For continuous variables, descriptive statistics (sample size, mean, SD, median, minimum, and maximum values) were determined. For discrete variables, the data were tabulated. A result was determined to be statistically significant if the accompanying statistical test yielded a P-value of 0.05 or less. Data from patients who experienced emesis were excluded from statistical analysis of PK parameters if vomiting occurred within 4 hours of drug administration.

The plasma PK parameters AUC, C_{24}, and oral clearance (CL/F) were summarized descriptively (geometric mean, 90% confidence interval [CI], and median). Differences between groups were determined using the t-test (one-way analysis of variance [ANOVA]) for continuous variables and Chi-Square test for nominal variables. Specifically, for comparison of all children to adults the t-test on loge transformed data was used. PK data for children were stratified by tablet integrity (crushed vs. whole) since children who could not swallow tablets may have been administered crushed tablets in suspension. These 2 subgroups of children were compared to adults using Fisher's least significant difference (LSD).

Data were natural log-transformed (log to base e) to determine if compared to the original scale, the groups' variances were more homogeneous and the distribution better approximated a normal distribution. If variances of groups were unequal, it was determined if log transformation

improved the homogeneity of the variances and the normality of the distribution. Natural log-transformed results were back-transformed to the original scale to report mean values.

Frequency distributions included plots of the data, distribution curves to test for normality, parametric and nonparametric measures of central tendency and dispersion, as well as the Shapiro-Wilk W test for normality. Coefficient of variation (CV) was calculated as (SD/mean) multiplied by 100%.

Patient covariates associated with AUC were explored with univariate analyses and combined into a full multivariate analysis of covariance (ANCOVA) model using backward elimination. Model terms with $P<0.05$ were retained in the final model to obtain estimates of significance for the remaining terms in the model.

The multivariate model for adjusted RPT AUC included 3 nominal groups of patients (children administered crushed tablets, children administered whole RPT tablets, and adults administered whole tablets), demographics (age, race, and gender), food consumed within 2 hours before or 1 hour after the RPT dose (food or no-food), and RPT mg/kg dosage groups. Data analyses were performed using NCSS 2007 and SAS®. Differences were deemed statistically significant if $P\leq0.05$.

Safety Assessment: Patients' clinical signs and symptoms during the 24 hours between drug administration and blood sampling were documented. The description and timing of meals, snacks, and concomitant medications relative to study drug dosing were also collected. Patients were examined to obtain body temperature and weight. Adverse events and SAEs were routinely reported as performed for TBTC Study 26 and not collected separately for this PK substudy other than those that may have occurred in the process of obtaining the single blood sample required. All reportable AEs encountered during the course of this PK substudy were recorded.

RESULTS

Study Population: A summary of patient disposition and datasets analyzed for the Study 26 PK substudy is provided in **Table 4**. Eighty-one of the 109 children eligible for the substudy and 80 adults were enrolled in the PK substudy. One child of the 81 enrolled was not included in the analysis because a PK sample could not be drawn. Three of the 80 adults were not included: in 2 patients the PK sample could not be drawn or insufficient sample volume was obtained, and 1 patient discontinued study drugs prior to PK blood draw. All 157 patients (80 children and 77 adults) who enrolled and had a blood sample collected were included in the PK Analysis Population.

Table 4. Patient Disposition and Datasets Analyzed

	Children (N=109)	Adults (N=80)	Total (N=189)
Enrolled	81	80	161
Analyzed	80	77	157
Age 2 – 4 years	40	NA	40
Age 5 – 8 years	22	NA	22
Age 9 – 11 years	18	NA	18
Adult (≥18 years)	NA	77	77

Abbreviation: NA=not applicable.
N represents the number of eligible patients.

Demographics:
A summary of the demographic and clinical characteristics of PK Analysis Population is provided in **Table 5**. An approximately equal number of males and females were enrolled in the PK substudy. Approximately three-quarters of the patient population were white and the median age of patients was 4 years (interquartile range 3 to 7.5 years) for children and 40 years (interquartile range 32 to 48 years) for adults. Of the 80 children analyzed in the PK substudy, 50% were between the ages of 2 to 4 years; 27.5% were between the ages of 5 to 8 years, and 22.5% were between the ages of 9 to 11 years. Statistically significantly more children were close contacts of a TB case (93.8%) than adults (76.6%; P=0.003) while statistically significantly more adults were recent TST converters (22.1% vs. 6.3%; P=0.005). At enrollment, 1 adult (1.3%) and no children were HIV infected.

Table 5. Demographic and Clinical Characteristics (PK Analysis Population)

Characteristic	Children N=80	Adult N=77	*P*-value
Indication for TLI, n (%)			
Close contact of TB case	75 (93.8)	59 (76.6)	0.003
Recent TST converter	5 (6.3)	17 (22.1)	0.005
HIV-infected	0 (0.0)	1 (1.3)	0.490
Fibrosis on chest radiograph	0 (0.0)	0 (0.0)	N/A
Age (years)			
Mean (standard deviation)	5.2 (3.0)	39.5 (11.7)	
Median (IQR)	4 (3 – 7.5)	40 (32 – 48)	<0.0001
Minimum	2	18	
Maximum	11	62	
Age, years, n (%)			
2-4	40 (50.0)	NA	NA
5-8	22 (27.5)	NA	NA
9-11	18 (22.5)	NA	NA
≥18	NA	77 (100.0)	NA
Gender, n (%)			0.715
Male	41 (51.3)	40 (52.0)	
Female	39 (48.8)	37 (48.1)	
Race, n (%)			
White	65 (81.3)	57 (74.0)	0.339
Black	11 (13.8)	16 (20.8)	0.293
Asian/Pacific Islander	4 (5.0)	4 (5.2)	1.000
Ethnicity (United States/Canada), n (%)			0.034
Hispanic	68 (85.0)	54 (70.1)	
Non-Hispanic	12 (15.0)	23 (29.9)	
TST size, mm (median, IQR)	13.5 (3 – 18)	16 (13 – 20)	0.01
Body mass index (median, IQR), kg/m^2	17 (16 – 19)	30 (26 – 33)	<0.0001

Note: *P*-value from Fisher Exact test.
Abbreviations: HIV=human immunodeficiency virus; TLI=treatment of latent tuberculosis infection; TB=tuberculosis; TST=tuberculin skin test; IQR=interquartile range; NA=not applicable; N/n=number; PK=pharmacokinetic.

Rifapentine Doses Administered: Of the patients analyzed in this PK substudy, RPT doses in children aged 2 to 11 years ranged from 300 to 900 mg based on the dosing algorithm used in children in the main study (**Table 1**). The RPT dose in adults was a fixed dose of 900 mg (1 patient with a body weight <45 kg received 750 mg). Descriptive statistics of doses administered to patients analyzed in this PK substudy in each age subgroup are presented in **Table 6**.

Table 6. Mean (SD) Rifapentine Dosage (PK Analysis Population)

	Mean (SD) Weight	Weight (Min-Max)	Mean (SD) Rifapentine Dosage		Range (Min-Max)	
	kg	kg	mg/kg	mg	mg/kg	mg
All children, n = 80	24.0 (12.5)	11.0 - 76.0	23.2 (4.3)	515.6 (165.1)	11.8 - 32.1	300 - 900
Age 2-4 years, n = 40	16.3 (4.7)	11.0 - 37.0	25.8 (3.4)	412.5 (94.6)	18.8 - 32.1	300 - 750
Age 5-8 years, n = 22	23.7 (7.7)	16.0 - 48.0	22.3 (3.2)	511.4 (110.1)	15.6 - 28.1	450 - 750
Age 9-11 years, n = 18	41.7 (11.4)	29.0 - 76.0	18.6 (2.9)	750.0 (89.1)	11.8 - 24.2	600 - 900
Adults >18 years, n = 77	86.1 (22.0)	49.0 - 168.0	11.0 (2.5)	898.1 (17.1)	5.4 - 16.7	750 - 900

Abbreviations: SD=standard deviation; n=number; Min=minimum; Max=maximum; PK=pharmacokinetic.

In Study 26, children who could not swallow tablets could have been administered a suspension of crushed RPT tablets and INH pills (alternatively, INH could have been administered in liquid form) in either a soft food or liquid. A comparison of RPT administration by tablet integrity is provided in **Table 7** and a summary of the number of patients administered crushed or whole tablets by age categories is provided in **Table 8**. Of the 80 children who were analyzed, 55 (69%) could not swallow tablets and were administered crushed RPT tablets, most of which (31/55, 56.4%) were aged 2 to 4 years (**Table 8**). The mean (SD) age of children administered whole tablets was 7.0 (3.1) years compared with a mean age of 5.1 (2.9) years for children administered crushed tablets (*P*=0.0088). All adults were administered whole tablets.

Table 7. Comparison of Rifapentine Administration by Tablet Integrity (Whole vs. Crushed) (PK Analysis Population)

Tablet Administration	Adults	Children	Mean (SD) Age in Years in Children	*P*-value
Crushed, n (%)	0 (0)	55 (69)	5.1 (2.9)	0.0088
Whole tablets, n (%)	77 (100)	25 (31)	7.0 (3.1)	NA

P-value based on t-test

Abbreviations: n=number; SD=standard deviation; NA=not applicable; PK=pharmacokinetic.

Table 8. Number of Children Administered Crushed or Whole Tablets by Age Categories (PK Analysis Population)

	Tablet Integrity		
Age Group (years)	Crushed N=55 n (%)	Whole N=25 n (%)	Total N=80 n (%)
2-4	31 (56.4)	9 (36.0)	40 (50.0)
5-11	24 (43.6)	16 (64.0)	40 (50.0)
5-8	15 (27.3)	7 (28.0)	22 (27.5)
9-11	9 (16.4)	9 (36.0)	18 (22.5)

Abbreviations: N/n=number; PK=pharmacokinetic.

Pharmacokinetics:

As shown in **Table 9**, RPT geometric mean (90% CI) $AUC_{0\text{-}inf}$ was 31% higher in children compared to adults. The geometric mean (90% CI) $AUC_{0\text{-}inf}$ in children administered crushed RPT tablets was lower than in children administered whole tablets (656 [607-708] vs. 884 [789-991] mcg*h/mL, respectively, P=0.0004) but still significantly higher than in adults (P=0.005).

Based on the ratios of geometric means for $AUC_{0\text{-inf}}$, relative exposure of RPT was 160% in children administered whole tablets, and 119% in children administered crushed tablets. The geometric mean RPT C_{24} was significantly greater with whole vs. crushed RPT tablets in children (P=0.001). Similar to $AUC_{0\text{-inf}}$, the ratios of the geometric means for C_{24} were higher in children administered whole tablets (166%; P<0.0001) and crushed tablets (114%) than in adults receiving 900 mg tablets; although the difference was not statistically significant (P=0.13). The ratios of geometric mean $AUC_{0\text{-inf}}$ of 25-desacetyl-RPT were similar to the parent RPT drug in children and adults.

When normalized by body weight, based on the ratio of the geometric mean, apparent oral clearance (CL/F/kg) was statistically significantly higher in children as compared to adults (49% higher; P<0.0001, **Table 9**) irrespective of tablet integrity and higher in the youngest children aged 2 to 4 years as compared to older children aged 5 to 11 years (41% higher; P<0.0001; **Table 10**). Results were similar for children administered crushed tablets and whole tablets: the ratio of the geometric mean CL/F/kg was 40% and 53% higher, respectively,

Exposure was lower in children 2 to 4 years of age compared with older children aged 5 to 11 years (*P*=0.07), but still higher than in adults (*P*=0.01). The geometric mean (90% CI) $AUC_{0\text{-inf}}$ in children 2 to 4 years of age was lower than in children aged 5 to 11 years (667 [596-747] vs. 776 [718-839] µg*h/mL, respectively (**Table 10**). Based on the ratios of geometric means for $AUC_{0\text{-inf}}$, relative exposure of RPT was 121% in children aged 2 to 4 years, and 141% in children aged 5 to 11 years relative to adults. Geometric mean $AUC_{0\text{-inf}}$ for the metabolite, 25-desacetyl-RPT, was similar to the parent RPT drug in both age groups of children and in adults (**Table 10**).

Table 9. Rifapentine and 25-Desacetyl-Rifapentine Pharmacokinetic Parameters by Tablet Integrity (PK Analysis Population)

	Children			Adults
	All children^ N=80	Whole Tablet N=25	Crushed Tablet N=55	N=77
Rifapentine				
$AUC_{0\text{-}inf}$ (mcg*h/mL)				
Geometric Mean (90% CI)	720 (674-769)	884 (789-991)	656 (607-708)	551 (516-588)
Median	759	872	657	553
%CV	0.38	0.26	0.39	0.36
RGM (90% CI) vs. adults; *P*-value (vs. adults)	1.31 (1.19-1.44) <0.0001	1.60 (1.41-1.83) <0.0001	1.19 (1.08-1.32) 0.005 {0.0004†}	Not applicable
C_{24} (mcg/mL)				
Geometric Mean (90% CI)	10.9 (10.0-12.0)	14.1 (12.1-16.6)‡	9.7 (8.7-10.8)‡	8.5 (7.8-9.3)
Median	12.4	14.1	10.4	8.3
%CV	0.57	0.33	0.61	0.48
RGM (90% CI), vs. adults; *P*-value (vs. adults)	1.28 (1.12-1.46) 0.002	1.66 (1.38-1.99) <0.0001	1.14 (0.99-1.31) 0.13 {0.001†}	Not applicable
CL/F (L/h)				
Geometric Mean (90% CI)	0.78 (0.73-0.84)	0.93 (0.82-1.04)	0.73 (0.67-0.79)‡	2.0 (1.91-2.19)
Median	0.78	0.84	0.73	2.0
%CV	0.42	0.52	0.32	0.32
RGM (90% CI), vs. adults; *P*-value (vs. adults)	0.38 (0.35-0.42) <0.0001	0.45 (0.40-0.52) <0.0001	0.36 (0.32-0.39) <0.0001 {0.0054†}	Not applicable
CL/F/kg (L/h/kg)				
Geometric Mean (90% CI)	0.036 (0.03, 0.04)	0.034 (0.03, 0.04)	0.037 (0.03, 0.04)	0.025 (0.02, 0.03)
Median	0.04	0.03	0.04	0.02
%CV	0.42	0.27	0.47	0.28
RGM (90% CI), vs. adults; *P*-value (vs. adults)	1.49 (1.36, 1.63) <0.0001	1.40 (1.26, 1.56) <0.0001	1.53 (1.36, 1.71) <0.0001	Not applicable
25-Desacetyl-Rifapentine Metabolite				
$AUC_{0\text{-}inf}$ (mcg*h/mL)				
Geometric Mean (90% CI)	735.0 (672-804)	843.4 (720-988)	690.5 (621-768)	521 (476-570)
Median	800	877	629	484
%CV	0.54	0.36	0.60	0.48
RGM, vs. adults; *P*-value (vs. adults)	1.41 (1.24-1.60) <0.0001	1.62 (1.35-1.94) <0.0001	1.33 (1.15-1.52) 0.0011 {0.085†}	Not applicable
C_{24} (mcg/mL)				
Geometric Mean (90% CI)	15.1 (13.5-16.8)	17.9 (15.6-20.5)	13.9 (12.1-16.1)	10.4 (9.5-11.4)
Median	17.8	20.0	13.8	10.0
%CV	0.63	0.41	0.70	0.52
RGM (90% CI), vs. adults; *P*-value (vs. adults)	1.45 (1.26-1.67) <0.0001	1.72 (1.44-2.06) <0.0001	1.34 (1.13-1.59) 0.005 {0.006†}	Not applicable

^*P*-value <0.01 vs. adults. ‡*P*-value by contrast t-test on $\log_e$ transformed data in comparison of all children vs. adults and by Fisher's LSD in each children's group (whole or crushed tablet) vs. adults. †*P*-value by Fisher's LSD for comparison between children administered whole vs. crushed rifapentine tablets.
Abbreviations: RGM=ratio of the geometric mean; CV=coefficient of variation; CI=confidence interval; CL/F=oral clearance; LSD=least significant difference; N=number; $AUC_{0\text{-}inf}$=area under the concentration-time curve from zero to time infinity; C_{24}=concentration 24 hours after drug ingestion; PK=pharmacokinetic.

Table 10. Rifapentine and 25-Desacetyl-Rifapentine PK Parameters in Children Aged 2 to 4 Years and 5 to 11 Years and in Adults (PK Analysis Population).

	Children		
	Age 2-4 years N=40	**Age 5-11 years N=40**	**Adults N=77**
Rifapentine			
$AUC_{0\text{-}inf}$ (mcg*h/mL)			
Geometric Mean (90% CI)	667 (596-747)	776 (718-839)	551 (516-588)
Median	717.6	765	553.0
%CV	0.44	0.30	0.36
RGM (90% CI), vs. adults;	1.21 (1.07-1.37)	1.41 (1.27-1.57)	NA
P-value (vs. adults)	0.01	<0.0001	
RGM (90% CI), vs. Children 5-11 yrs	0.86 (0.75, 0.98)	NA	NA
P-value (vs. Children 5 – 11 yrs)	0.07		
C_{24} (mcg/mL)			
Geometric Mean (90% CI)	9.6 (8.2-11.4)	12.2 (11.1-13.7)	8.5 (7.8-9.3)
Median	11.0	12.7	8.3
%CV	0.68	0.41	0.48
RGM (90% CI), vs. adults;	1.13 (0.94-1.36)	1.45 (1.26-1.67)	NA
P-value (vs. adults)	0.27	<0.0001	
CL/F (L/h)			
Geometric Mean (90% CI)	0.68 (0.62-0.74)	0.90 (0.80-1.01)	2.0 (1.91-2.19)
Median	0.67	0.96	2.0
%CV	0.33	0.46	0.32
RGM (90% CI), vs. adults;	0.33 (0.30-0.37)	0.44 (0.39-0.50)	NA
P-value (vs. adults)	<0.0001	<0.0001	
CL/F/kg (L/h/kg)			
Geometric Mean (90% CI)	0.043 (0.04, 0.05)	0.031 (0.028, 0.034)	0.025 (0.02, 0.03)
Median	0.04	0.03	0.02
%CV	0.37	0.38	0.28
RGM (90% CI), vs. adults;	1.77 (1.59, 1.97)	1.25 (1.12, 1.40)	NA
P-value (vs. adults)	<0.0001	0.001	
RGM (90% CI), vs. Children 5-11 yrs;	1.41 (1.23, 1.62)	NA	NA
P-value (vs. Children 5 – 11 yrs)	<0.0001		
25-Desacetyl-Rifapentine Metabolite			
$AUC_{0\text{-}inf}$ (mcg*h/mL)			
Geometric Mean (90% CI)	695 (599-807)	777 (691-874)	521 (478-568)
Median	844	776	484.3
%CV	0.61	0.47	0.48
RGM (90% CI), vs. adults;	1.33 (1.14-1.56)	1.49 (1.29-1.73)	NA
P-value (vs. adults)	0.003	<0.0001	
C_{24} (mcg/mL)			
Geometric Mean (90% CI)	14.4 (12.0-17.3)	15.7 (13.9-17.8)	10.4 (9.5-11.4)
Median	19.1	16.0	10.0
%CV	0.76	0.50	0.52
RGM (90% CI), vs. adults;	1.39 (1.14-1.70)	1.51 (1.30-1.77)	NA
P-value (vs. adults)	0.009	<0.0001	

Abbreviations: CI=confidence interval; CL/F=oral clearance; CV=coefficient of variation; N=number; $AUC_{0\text{-}inf}$=area under the concentration-time curve from zero to time infinity; C_{24}=concentration 24 hours after drug ingestion; PK=pharmacokinetic; NA=not applicable; yrs=years; RGM=ratio of the geometric mean.

In patients who received the correct RPT dose based on weight band, RPT geometric mean (90% CI) AUC was highest in the 32.1-50.0 kg weight band compared to the >50 kg weight band and the 10.0-14.0 kg weight band (**Table 11**). The 10.0-14.0 kg weight band was comprised of 13 children, all of whom received crushed tablets and presented with the lowest exposure; the 32.1-50.0 kg weight band was comprised of 15 children (crushed tablets, N=8) and 1 adult, and the >50 kg weight band was comprised of 76 adults and 3 children (crushed tablets, N=1). Thus, the lowest weight bands (10.0-14.0 kg and 14.1-25.0 kg) received higher geometric mean doses based on mg/kg (23.6 mg/kg and 25.3 mg/kg, respectively) compared to the highest weight band (>50 kg: 10.8 mg/kg). The results for the metabolite, 25-desacetyl-RPT, were similar to the parent RPT drug. Moderate inter-patient variation in $AUC_{0\text{-}inf}$ was observed in all weight bands (**Figure 1**).

Table 11. RPT AUC by Weight Band and Tablet Integrity (Crushed or Whole)

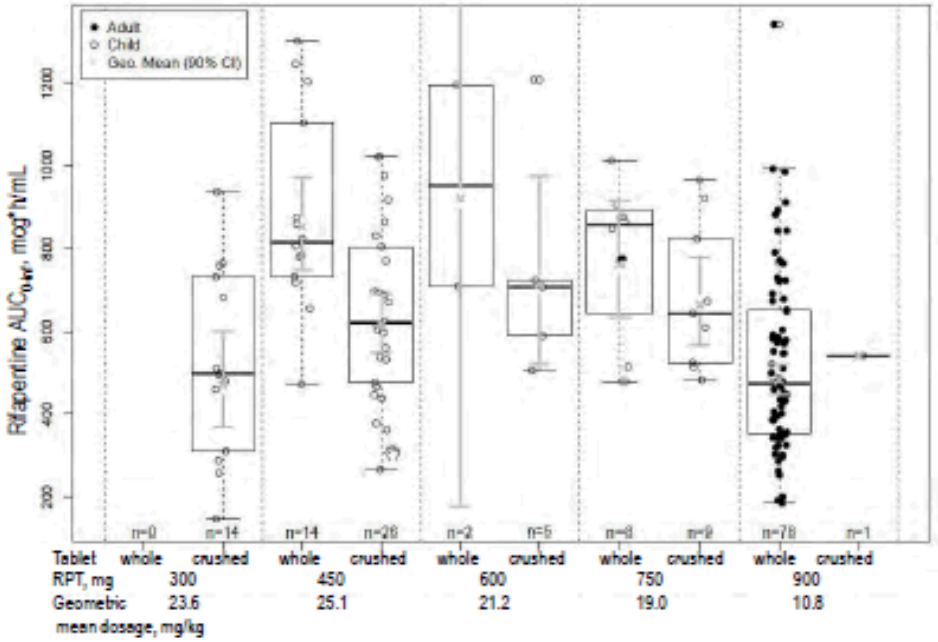
Weight Band (kg)	Age Group	RPT Dose (mg)	N	Tablet Integrity	Geometric Mean of RPT mg/kg[a]	RPT AUC (mcg*h/mL)						
						Geometric Mean RPT AUC (90% CI)	CV	Min	25th Percentile	Median	75th Percentile	Max
10.0-14.0	Child	300	13	Crushed	23.6	504 (399-637)	0.5	184.7	375.7	489.9	706.5	989.3
14.1-25.0	Child	450	26	Crushed	25.3	744 (684-810)	0.32	365.7	584.4	765.9	968.1	1301.4
		450	13	Whole								
25.1-32.0	Child	600	4	Crushed	21.3	762 (558-1041)	0.34	545	637.4	746.5	765.5	1297
		600	1	Whole								
32.1-50.0	Adult	750	1	Whole	18.7	813 (721-916)	0.28	539.5	615.6	883.9	1022.4	1184.2
	Child	750	8	Crushed								
		750	7	Whole								
>50	Adult	900	76	Whole	10.8	551 (517-588)	0.35	263.6	440.1	554.6	733.5	1300.7
	Child	900	1	Crushed								
		900	2	Whole								

Abbreviations: RPT=rifapentine; AUC=area under the concentration-time curve; Min=minimum; Max=maximum; N=number [of patients]; CI=confidence interval; CV=coefficient of variation

Note: Table based on those participants who received the correct RPT dose for their weight band. Children that did not receive the correct RPT dose based on their weight band were removed. These include: 1 child in weight band 10.0-14.0 kg who received RPT 450 mg; 1 child in weight band 14.1-25.0 kg who received RPT 600 mg; 2 children in weight band 25.1-32.0 kg, where 1 received RPT 450 mg and the other received RPT 750 mg; and 1 child in weight band 32.1-50.0 kg who received RPT 600 mg. Data for all patients are included in Table 14.5.1.

[a]Geometric Mean RPT mg/kg by RPT dose.

Figure 1. Rifapentine AUC0-inf by Rifapentine Dose (mg) and Tablet Integrity (Crushed or Whole) (PK Analysis Population)



In contrast to RPT AUC0-inf without adjustment for dosage, geometric mean (90% CI) dose-normalized AUC0-inf was greater in adults compared to all children and to children administered crushed tablets (adults vs. all children dose-normalized AUC0-inf, 51.3 [48.0, 54.8] vs. 31.6 [29.5, 33.8] µg*h/mL/mg/kg, P<0.0001). Also, dose-normalized geometric mean (90% CI) AUC0-inf was significantly greater in children administered whole tablets versus crushed tablets (41.6 [38.2, 45.4] vs. 27.9 [25.2, 30.8] µg*h/mL/mg/kg, respectively; *P*<0.0001). There was a positive modest association in children between age and dose-normalized RPT AUC0-inf (Spearman's r=0.54, *P*<0.0001).

As shown in **Table 12**, food increased RPT AUC0-inf by approximately 25 and 41% in children and adults, respectively. Although the exposures are increased with food in both children and adults, the difference in geometric mean RPT AUC was statistically significant only for adults (*P*<0.0001).

Table 12. Comparisons of the Geometric Mean Rifapentine AUC in Both Children and Adults When Administered With and Without Food (PK Analysis Population)

Population	N	Geometric Mean RPT AUC (mcg*h/mL)	CV	Min	Max	90% CI	*P*-value*
Child with Food	70	740.3	0.34	283.0	1333.7	(693.1, 790.8)	0.23
Child with no Food	10	590.2	0.59	184.7	1095.5	(430.5, 809.0)	
Adult with Food	53	613.8	0.33	273.7	1300.7	(570.2, 660.8)	<0.0001
Adult with no Food	24	434.3	0.29	263.6	847.2	(393.3, 479.6)	

*P-value based on t-test using lognormal transformation.
Abbreviations: AUC=area under the concentration time curve; CI=confidence interval; Min=minimum; Max=maximum; N=number; CV=coefficient of variation; RPT=rifapentine; PK=pharmacokinetic.

Nine (90%) of 10 children who took drug without food and 69 (99%) of 70 children who took drug with food had RPT AUC greater than 80% of the geometric mean RPT $AUC_{0\text{-inf}}$ of adults who took drug without food (lowest exposure observed).

In children <5 years of age (n=40), most children reached between 80% and 200% of the geometric mean adult RPT exposure (29 children [72.5%]); 6 (15.0%) children and 5 (12.5%) children, respectively, had exposures <80% and >200% of the geometric mean adult RPT exposure. In the 5- to 11-year age group, 90% of children reached between 80% and 200% of the geometric mean adult RPT exposure, while 1 (2.5%) child reached <80% and 3 (7.5%) children reached >200% of the geometric mean adult RPT exposure.

In children who weighed between 10.0 and 14.0 kg (n=14), 10 (71.4%) reached between 80% and 200% of the geometric mean adult RPT exposure, while 4 (28.6%) reached <80% of the geometric mean adult RPT exposure. In the 14.1- to 25.0-kg weight band (n=40), 80% of children reached between 80% and 200% of the geometric mean adult RPT exposure, while 3 (7.5%) children reached <80% and 5 (12.5%) children reached >200% of the geometric mean adult RPT exposure.

In the higher weight-band groups (25.1 kg to 32.0 kg and 32.1 kg to 50 kg), the majority of children reached between 80% and 200% of the geometric mean adult RPT exposure. Two children in the 25.1- to 32.0-kg group and 1 child in the 32.1- to 50-kg group were above 200% of the geometric mean adult RPT exposure. All 3 children who weighed >50 kg achieved between 80% and 150% of the geometric mean adult RPT exposure.

Of the 55 children enrolled in the PK substudy who were administered crushed tablets, 46 (84%) achieved at least 80%, but less than 200%, of the geometric mean adult RPT exposure. The children who achieved the lowest exposure (<80% of the geometric mean adult RPT exposure; n=7) were mostly aged 2 to 4 years and were the lightest children (≤25.0 kg). The children who achieved the highest exposure (>200% of the mean adult RPT exposure; n=2) were aged 2 to 4 years (**Table 13**).

As shown in **Table 13**, among the 7 children who reached <80% of the adult exposures, 2 patients (17-8108 and 40-8064) had very low RPT concentrations (less than 70%). In these 2 patients (both aged 2 to 4 years) RPT was administered as crushed tablets in slurry, it is speculated that the complete dose was not administered, which could have contributed to the low concentrations. Among the 8 patients who reached >200% of the adult exposures, none exceeded 250%.

Table 13. Listing of Children Reaching <80% and >200% of the Geometric Mean Adult RPT Exposure (PK Analysis Population)

Patient ID	Age (years)	Weight Band (kg)	RPT AUC (mcg*h/mL)	Percentage of Geometric Mean Adult Exposure	Desacetyl RPT Metabolite AUC (mcg*h/mL)	Crushed/Whole Tablets
17-8108	2	>10-14	283.03	<80%	228.33	Crushed
20-7435	2	>10-14	375.73	<80%	547.80	Crushed
20-8069	3	>14-25	428.44	<80%	318.59	Crushed
40-8064	4	>10-14	184.69	<80%	139.61	Crushed
40-8079	2	>10-14	368.62	<80%	362.95	Crushed
63-8096	5	>14-25	365.71	<80%	273.38	Crushed
70-7747	4	>14-25	435.53	<80%	397.40	Crushed
17-7599	4	>14-25	1121.00	>200%	1052.40	Whole
20-7571	3	>14-25	1141.50	>200%	1751.90	Crushed
22-7078	4	>14-25	1181.80	>200%	1012.10	Whole
40-6960	4	>14-25	1301.40	>200%	1407.10	Whole
40-6971	12	>25-32	1333.70	>200%	1338.00	Whole
40-7038	12	>35-50	1184.20	>200%	1422.90	Whole
40-7143	4	>25-32	1297.00	>200%	1511.60	Crushed
40-7637	8	>14-25	1212.60	>200%	629.39	Whole

Abbreviations: AUC=area under the concentration-time curve; ID=identification; RPT=rifapentine; PK=pharmacokinetic.

Mixed Model Analysis:
In the final mixed model, all covariates were eliminated leaving only cofactors (crushed tablets vs. whole tablets, food vs. no food, and RPT mg/kg dosage groups). In this final mixed model (ANOVA), mean RPT $AUC_{0\text{-}inf}$ adjusted for other factors significantly increased in children with administration of RPT with whole (vs. crushed) tablets, and in adults with administration of whole RPT tablets with food (vs. without food) (**Table 14**).

As shown in **Table 14**, a significant global dose effect regarding exposure was observed (P=0.02). Adjusted mean $AUC_{0\text{-}inf}$ in children in either dose group (either by dosage range or weight band) who received less than 900 mg was not statistically significantly different than adults. However, the adjusted mean $AUC_{0\text{-}inf}$ was consistently statistically significantly lower in the lightest children (11-14 kg) who received the lowest dose (300 mg) than in the other child dose groups.

Adjusted mean RPT $AUC_{0\text{-}inf}$ with food was significantly greater than without food in all patients (728 vs. 552 µg*h/mL, P<0.0001, ANOVA main effect). Adjusted mean RPT $AUC_{0\text{-}inf}$ was significantly lower in children receiving crushed tablets compared to children receiving whole tablets (P=0.006) but not different than adults.

Table 14. Final Mixed Model ANOVA with RPT AUC Adjusted for Factors With a Significant Effect (PK Analysis Population)

Factors in the final, mixed model ANOVA, n=157	**N**	**Adjusted* Mean of $AUC_{0\text{-inf}}$ (mcg*h/mL)**	***P*-value**
Group Effect			P=0.02
1 – Child - Crushed	55	586	0.006 1 vs. 2
2 – Child - Whole	25	735	0.96 1 vs. 3
3 – Adult - Whole	77	591	0.18 2 vs. 3
			P=0.70 3 vs. 1 and 2
Food Effect			*P*<0.0001
Food	123	728	NA
Fasting	34	552	NA
Dose (dosage range; weight band) Group Effect			*P*=0.02**
1 – 300 (21-27 mg/kg; 11-14 kg)	13	506	0.60 1 vs. 5
2 – 450 (17-32 mg/kg; 14-27 kg)	41	673	0.27 2 vs. 5
3 – 600 (18-24 mg/kg; 25-33 kg)	7	733	0.18 3 vs. 5
4 – 750 (15-24 mg/kg; 31-49 kg)	17	731	0.11 4 vs. 5
5 – 900 (5-17 mg/kg; 53-168 kg)	79	559	Group 5 0.007 2 vs. 1 0.015 3 vs. 1 0.003 4 vs. 1

Abbreviations: ANOVA=analysis of variance; AUC=area under the concentration-time curve; $AUC_{0\text{-inf}}$=area under the concentration-time curve from zero to time infinity; RPT=rifapentine; N/n=number; NA=not applicable; PK=pharmacokinetic.
*Estimate of RPT AUC by analysis of variance of ln transformed data adjusted for other factors in the final model where possible and back transformed to the original scale.
***P*-value by Fisher's least significant difference for pairwise comparisons of groups and contrast t-test for adults vs. children.

As shown in **Table 15**, on average, after adjusting for food intake and tablet integrity, the dose-normalized RPT $AUC_{0\text{-inf}}$ for children taking 300 mg RPT was 21 mcg*h/mL less compared to adults taking 900 mg RPT, and for children taking 450 mg RPT was 17 mcg*h/mL less compared to adults taking 900 mg. These differences were significant (*P*<0.0001). For the higher RPT doses of 600 and 750 mg there were no differences when compared with the 900-mg dose.

Table 15. Comparison of Dose-Normalized RPT $AUC_{0\text{-inf}}$ by RPT Dose After Adjusting for Food Intake and Tablet Integrity (PK Analysis Population)

RPT Dose	**Estimated Difference of Dose-Normalized RPT $AUC_{0\text{-inf}}$ between 900 mg Dose and All Other RPT Dose Groups (mcg*h/mL)**	**Standard Error**	***P*-value[a]**
300 mg	-21.01	5.11	<0.0001
450 mg	-17.66	3.41	<0.0001
600 mg	-9.03	5.72	0.1167
750 mg	-5.53	3.85	0.1529
900 mg			

Abbreviations: RPT=rifapentine; ANCOVA=analysis of covariance; $AUC_{0\text{-inf}}$=area under the concentration-time curve from zero to time infinity; PK=pharmacokinetic.
[a]Based on ANCOVA.

Safety:
Among the 157 patients who were analyzed in the PK substudy, 10 patients (including 7 adults and 3 children) reported 11 AEs during the main study, none of which was reported to be a serious AE. Most events were mild or moderate; 3 severe events were reported including 1 event each of back pain, dyspnea, and hypersensitivity. With the exception of urinary tract infection reported in 2 patients, all events were reported in 1 patient each. No AEs or serious AEs were reported in association with the single blood draw required for this PK substudy. Three patients (1 child and 2 adults) enrolled in the PK substudy discontinued the main study due to an AE considered related to study medications. AEs leading to treatment discontinuation included drug intolerance, hypersensitivity, and dyspnea in 1 patient each (**Table 16**).

Table 16. Listing of Adverse Events (PK Analysis Population)

Patient Number	Age (years)	Doses Taken	PK Sample Date	PK Dose	PK Dose Date	Onset Date	MedDRA Preferred Term	Grade	Relationship	Discontinuation Due to AE
17-7642	4	9	06NOV2007	09	05NOV2007	16NOV2007	Decreased appetite	1	Unlikely	No
17-7940	49	11	30JAN2008	03	29JAN2008	22JAN2008	Joint swelling	2	Unlikely	No
20-7397	41	12	01AUG2007	07	31JUL2007	11AUG2007	Back pain	3	Not related	No
40-6972	36	12	08MAR2007	04	07MAR2007	16MAR2007	Urinary tract infection	2	Not related	No
40-7143	4	7	04MAY2007	03	03MAY2007	14JUN2007	Urinary tract infection	2	Not related	No
			04MAY2007	03	03MAY2007	05JUN2007	Drug intolerance	1	Definite	Yes
40-7158	33	5	02MAY2007	04	01MAY2007	09MAY2007	Dyspnoea	3	Definite	Yes
40-7362	23	5	27JUN2007	03	26JUN2007	11SEP2007	Hypersensitivity	3	Definite	Yes
40-8017	27	4	20FEB2008	03	19FEB2008	04MAR2008	Pregnancy	NA	Unclassifiable	No
54-8001	42	12	05MAR2008	05	04MAR2008	25MAR2008	Hyperkeratosis	2	Possible	No
54-8072	2	12	22APR2008	06	21APR2008	11JUL2008	Sinusitis	2	Unlikely	No

Abbreviations: PK=pharmacokinetic; MedDRA=Medical Dictionary for Regulatory Activities; AE=adverse event; NA=not applicable

The treatment-related AE rate per event in children aged 2 to 11 years who were analyzed in the PK substudy and in those who were enrolled in the study 26 by the same sites during the PK substudy period but were not recruited into the PK substudy was similar (1.3% vs. 4.0%, respectively; *P*=0.421).

Table 17. Incidence of Adverse Events in Children Aged 2 to 11 Years Who Were Analyzed in the PK Substudy and in Those Who Were Not Recruited into the PK Substudy

	Children Age 2-11 Years (Enrolled in 3RPT/INH Arm)			
Calculated Rates	Not Recruited into PK Substudy N=25 n (%)	Analyzed in PK Substudy N=80 n (%)	Total N=105 n (%)	*P*-value[a]
AE rate per patient	3 (12.0)	3 (3.8)	6 (5.7)	0.145
AE rate per event	4 (16.0)	4 (5.0)	8 (7.6)	0.09
Treatment-related AE rate per event	1 (4.0)	1 (1.3)	2 (1.9)	0.421
Discontinuation from the treatment trial due to AE per patient with AE(s)	0 (0.0)	1 (1.3)	1 (1.0)	1.000

Abbreviations: AE=adverse event; PK=pharmacokinetic; N/n=number; 3RPT/INH=3-month (12-dose) regimen of weekly rifapentine and isoniazid.
Note: Table includes all children 2-11 years enrolled between 04 May 2005 and 24 Jul 2008 from study sites 17, 20, 22, 24, 40, 54, 63, and 70.
[a]*P*-value based on Fisher's exact test.

SPONSOR'S CONCLUSIONS

- In this PK substudy, rifapentine $AUC_{0\text{-}inf}$ was 31% higher in children (aged 2 to 11 years) receiving on average 2-fold higher mg/kg than in adults receiving a standard 900-mg dose. The geometric mean (90% CI) $AUC_{0\text{-}inf}$ was 720 (674-769) µg*h/mL in children irrespective of ages and weights compared with 551 (516-588) µg*h/mL (P<0.0001) in adults.
- Exposure was lower in children 2 to 4 years of age than in older children aged 5 to 11 years, but still higher than in adults (P=0.01). The geometric mean (90% CI) $AUC_{0\text{-}inf}$ in children 2 to 4 years of age was 667 (596-747) µg*h/mL compared with 776 (718-839) µg*h/mL in children 5 to 11 years of age (P=0.07).
- Based on the ratios of geometric means for $AUC_{0\text{-}inf}$, relative exposure of RPT vs. adults was 121% in children aged 2 to 4 years, and 141% in children aged 5 to 11 years.
- $AUC_{0\text{-}inf}$ for the active metabolite 25-desacetyl RPT was similar to the parent RPT compound.
- The geometric mean (90% CI) $AUC_{0\text{-}inf}$ in children administered crushed RPT tablets was lower than in children administered whole tablets (656 [607-708] vs. 884 [789-991] µg*h/mL, respectively (P=0.0004) but still higher than in adults (551 [516-588] µg*h/mL).
- Adjusted mean RPT $AUC_{0\text{-}inf}$ with food was significantly greater than without food using a mixed model analysis (728 vs. 552 µg*h/mL, respectively, P<0.0001, ANOVA main effect) in the PK population.
- In at least 90% of children in this substudy, RPT $AUC_{0\text{-}inf}$ was greater than 80% of the geometric mean adult value (the minimum targeted exposure). However, in 9% of children (mainly from the younger age group [2 to 4 years]), RPT AUC0-inf values were lower than 80% of the geometric mean adult value, and 10% of children reached exposures above 200% of the geometric mean adult value, without exceeding 250%.
- Based on the ratio of the geometric mean, apparent oral clearance per kilogram of body weight (CL/F/kg) was statistically significantly higher in children as compared to adults, (49% higher; P<0.0001) and higher in the youngest children aged 2 to 4 years as compared to the older ones (aged 5 to 11 years) (41% higher, P<0.0001) Results were similar for children administered crushed tablets and whole tablets, the ratio of the geometric mean was 53% and 40% higher, respectively, than adults (P<0.0001).
- There was no correlation between the levels of RPT exposure obtained in this substudy in children using the higher weight-based dosing algorithm and the incidence or severity of AEs during treatment with RPT.
- Use of higher weight-based RPT dosages for young children, as implemented in Study 26, is warranted in order to achieve adequate RPT systemic exposures that in adults have been associated with successful and well tolerated treatment of LTBI.

Reviewer Assessment: The Sponsor's conclusions are appropriate based on study results.

Safety:

Among 8 pediatric patients who achieved >200% of the adult exposure, only subject 40-7143 experienced an adverse event (Grade 2 urinary tract infection), which was considered not related to the test drug (RPT/INH). Despite approximately 30% increase in rifapentine AUC in children compared to adults, no death and serious adverse events were reported in children. In addition,

no relationship between rifapentine exposure and incidence and severity of adverse events were observed.

Efficacy:
The primary outcome used to determine effectiveness is the development of culture-confirmed TB disease in patients ≥18 years and the development of culture-confirmed or probable (clinical) TB disease in patients <18 years old within 33 months of study enrollment.

In the MITT population at 33 months after enrollment in the TBTC-S26 main study (30 months after 3RPT/INH treatment and 24 months after 9INH treatment), TB disease (culture confirmed) developed in 7 of 3986 patients in the 3RPT/INH treatment arm (cumulative rate, 0.19%) and in 15 of 3745 patients in the 9INH treatment arm (cumulative rate, 0.43%), for a difference of -0.24% with an upper limit of the 95% CI of +0.01%, which is smaller than the non-inferiority margin of +0.75%.

The results of the analysis of development of TB disease in the pediatric population were consistent with the TBTC-S26 main study population. Three children under 18 years old developed TB disease, including a 2-year-old male (clinical TB), a 5 year-old male (clinical TB), and a 14-year-old female (culture-confirmed TB), all enrolled in the 9INH arm, resulting in cumulative TB event rates of 0.78% for the 9INH arm and 0% for the 3RPT/INH arm. All 3 children who developed TB disease were enrolled in the main study and are also included in the analysis for the main study.

In the TBTC S26 pediatric PK substudy, 7 children (mostly aged 2-4 years) who received crushed RPT tablets had RPT AUC less than 80% of that in adults. However, no pediatric patients on the 3RPT/INH arm developed TB disease over the 33-month follow-up period.

Conclusion:
Results from this PK substudy demonstrated that RPT exposure was not equivalent between children (ages 2 to 11 years) receiving weight-based dosing and adults receiving RPT 900 mg. The dosing algorithm used in Study 26 in children (aged 2 to 11 years) produced 31% higher RPT exposures in most children compared to mean RPT exposures in adults receiving a standard 900-mg dose. RPT exposures were 60% and 19% higher in children administered whole tablets and crushed tablets, respectively, compared to adults. The minimum targeted exposure was defined as 80% of the geometric mean exposure of all adults enrolled and receiving a 900-mg RPT dose. Approximately 90% of the enrolled children achieved exposures above the minimum targeted adult exposures. Seven (7) children who had RPT exposures less than the minimum targeted adult exposures were mostly aged 2-4 years and received RPT as crushed tablets. Eight (8) patients achieved > 2-fold, but < 2.5-fold, of the mean adult RPT exposure.

The proposed weight-based dosing regimen was used in the pediatric patients (ages 2-11 years) enrolled in the TBTC Study 26. Despite the generally increased exposure observed in children 2 to 11 years of age in this PK substudy, an increase in the incidence or severity of adverse events (AEs) was not observed and no SAEs were reported in any patients who participated in the PK substudy. The frequency of treatment-related AEs in Study 26 was similar for children enrolled in and not enrolled in the PK substudy (1.3% vs. 4.0%, respectively; p=0.421). In addition,

although >20% decrease in RPT exposure, compared to adults, was observed in 7 younger children (mostly aged 2-4 years) who received crushed tablets, an decrease in efficacy was not observed as no pediatric patients on the 3RPT/INH arm in study 26 developed TB disease over the 33-month follow-up period (primary clinical outcome). Therefore, the proposed pediatric dosing recommendations are supported by observations from TBTC Study 26.

Taken together, from a clinical pharmacology perspective, the weight-based dosing algorithm used in Study 26 appears appropriate for both safety and efficacy in pediatric patients (2-11 years) with LTBI.

STUDY NO.: INT12291

An open-label, non-randomized, single sequence, two periods, four-treatment, three parallel groups pharmacokinetic interaction study of repeated oral doses (daily or weekly regimen) of rifapentine on ATRIPLA™ (fixed dose combination of efavirenz, emtricitabine, and tenofovir disoproxil fumarate) given to HIV+ patients (INT12291)

Date(s): 14 December 2012 to 03 June 2013
Sponsor: SANOFI AVENTIS US LLC
Clinical Site: Buffalo Clinical Research Center, LLC, Buffalo, New York 14202 USA

OBJECTIVE(S):

- Primary: To evaluate the effect of single and repeated administration of rifapentine given as daily or weekly regimen on steady state pharmacokinetics (PK) parameters of efavirenz, emtricitabine, and tenofovir given as a fixed dose combination (ATRIPLA).
- Secondary: To evaluate the safety and tolerability of concomitant administration of rifapentine and ATRIPLA given to HIV+ patients.

METHODS

Study Design: This is an open-label, nonrandomized, 2-period, 4-treatment, 3 parallel cohorts in a single sequence study:

- 1st cohort: ATRIPLA in Period 1 (15 days) and ATRIPLA + 15 mg/kg once daily x 21 days of oral rifapentine in Period 2.
- 2nd cohort: ATRIPLA in Period 1 (15 days) and ATRIPLA + 900 mg oral of rifapentine (once weekly – 3 weekly administrations) in Period 2.
- 3rd cohort (optional): ATRIPLA in Period 1 (15 days) and ATRIPLA + 10 mg/kg twice daily x 21 days of oral rifapentine in Period 2.

This study report only summarized results for the weekly regimen – 2nd cohort.

Study Treatment:

PRIFTIN™ rifapentine

Formulation: 150-mg film-coated tablet
Route of administration: oral
Dose regimen: 900 mg once weekly (Days 1, 8, and 15) for 3 weekly administrations in fed conditions in the morning.
Batch number: C1025766 / A1011

ATRIPLA

Formulation: film-coated tablet (600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate corresponding to 245 mg tenofovir disoproxil given as a fixed dose combination)
Route of administration: oral
Dose regimen: All patients must have been on the same dose and dosing schedule for ATRIPLA during all study periods. All patients should have been on ATRIPLA before the screening (background therapy) and received 1 tablet at least 2 hours after the evening meal (fasting conditions), at night (bedtime) each day of the study.

Batch number(s): 000673

Duration of observation: Approximately 60 days (including a screening period of up to 21 days prior to dosing, 15 days in treatment Period 1, 18 days in treatment Period 2, and follow-up visits up to 5 days after dosing).

Inclusion/Exclusion Criteria: HIV-infected male and female patients (treated by ATRIPLA) between 18 and 55 years of age, inclusive; Body weight between 50.0 and 110.0 kg, inclusive, if male, and between 40.0 and 100.0 kg, inclusive, if female; body mass index between 18.0 and 35.0 kg/m^2, inclusive; with a CD4 cell count of at least 350 and with a viral load below the limit of detection.

Any medication (including St John's Wort) within 14 days before inclusion or within 5 times the elimination half-life or pharmacodynamic half-life of the medication were prohibited, with the exception of ATRIPLA, multivitamins, acetaminophen (up to 650 mg every 6 hours as an analgesic), ibuprofen (up to 600 mg BID), naproxen (up to 500 mg BID for pain or headache), Bactrim™ (sulfamethoxazole and trimethoprim), and Valtrex™ (valacyclovir).

PK Sample Collection:

- Plasma samples were collected predose on Day 1 and 8 hours postdose on Days 1, 8, and 15 for the determination of rifapentine and 25-desacetyl rifapentine.
- Plasma samples were collected predose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 16, and 24 hours postdose of ATRIPLA on Day -2 (Period 1), Day 1 (Period 2), and Day 16 (Period 2) for the determination of efavirenz, emtricitabine, and tenofovir.

Analytical Methods:

- Plasma concentrations of rifapentine and 25-desacetyl rifapentine were determined using a validated liquid chromatography-tandem mass spectrometry method with a lower limit of quantification of 1.00 µg/mL for both analytes (**Table 1**).
- Plasma concentrations of efavirenz, emtricitabine, and tenofovir were determined simultaneously using a validated liquid chromatography-tandem mass spectrometry method with lower limit of quantifications of 10, 5, and 2.5 ng/mL, respectively (**Table 2**).

Table 1. Bioanalytical results of rifapentine and 25-desacetyl rifapentine in plasma

Criterion	Rifapentine	25-desacetyl Rifapentine	Reviewer Comments
Calibration Range	1-100 µg/mL	1-100 µg/mL	*Satisfactory*
LLOQ	1 µg/mL	1 µg/mL	*Satisfactory*
Linearity, R^2	≥0.9900	≥0.9941	*Satisfactory*
Accuracy, %	Within ±4.8	Within ±2.50	*Satisfactory*
Precision, CV	≤ 8.90%	≤ 6.87%	*Satisfactory*
Quality Control	3, 50, 80 µg/mL	3, 50, 80 µg/mL	*Satisfactory*
Accuracy, %	Within ± 7.88	Within ± 5.20	*Satisfactory*
Precision, CV	≤ 8.14%	≤ 9.58%	*Satisfactory*
Stability	Rifapentine and 25-desacetyl rifapentine are stable in matrix for at least 24		*Satisfactory*

	hours at room temperature or +4°C, after three additional freeze/thaw cycles at -20°C or -80°C, after at least 110 days at -20°C or -80°C for rifapentine. For 25-desacetyl rifapentine long term stability in matrix is demonstrated within the range of the calibration curve for at least 110 days at -20°C or -80°C. Diluted samples out of range up to 100 µg/mL are stable for up to 44 days at -20°C or -80°C. Diluted samples out of range up to 25 µg/mL are stable for up to 69 days at -20°C or -80°C. Rifapentine and 25-desacetyl rifapentine are also stable in extract for at least 96 hours at +5°C. 25-desacetyl rifapentine is stable in blood at +4°C for at least 4 hours. Rifapentine is stable in blood at +4°C for up to 2 hours only.	

Table 2. Bioanalytical results of efavirenz, emtricitabine, and tenofovir in plasma

Criterion	Efavirenz	Emtricitabine	Tenofovir	Reviewer Comments
Calibration Range	10-10000 ng/mL	5-5000 ng/mL	2.5-2500 ng/mL	*Satisfactory*
LLOQ	10 ng/mL	5 ng/mL	2.5 ng/mL	*Satisfactory*
Linearity, mean R^2	≥0.9939	≥0.9947	≥0.9954	*Satisfactory*
Accuracy	Within ±2.00%	Within ±2.00%	Within ±1.60%	*Satisfactory*
Precision, CV	≤8.72 %	≤8.42 %	≤5.89%	*Satisfactory*
Quality Control	30, 5000, 8000 ng/mL			*Satisfactory*
Accuracy	Within ±2.80%	Within ±2.00%	Within ±2.50%	*Satisfactory*
Precision, CV	≤10.23 %	≤7.87%	≤10.59%	*Satisfactory*
Stability	Efavirenz, emtricitabine and tenofovir are stable in human plasma after 24 hours on benchtop at room temperature and after three additional freeze/thaw cycles at -20°C and -80°C and at least 162 days at -20°C and -80°C. Viability of the extracted samples in the autosampler vial tray is demonstrated at +15°C up to 96 hours. Stability in whole blood is proven for 2 hours on ice bath for the three compounds and at room temperature for efavirenz and tenofovir only.			*Satisfactory*

Pharmacokinetic Assessment:

Primary endpoints:

Efavirenz, emtricitabine, and tenofovir: C_{min} (minimum plasma concentration observed), C_{max} (maximum plasma concentration observed), AUC_{0-24} (area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval [24 hours])

Secondary endpoints:

Efavirenz, emtricitabine, and tenofovir: tmax (time to reach C_{max}), $t_{1/2z}$ (terminal half-life associated with the terminal slope), CL_{ss}/F (apparent total body clearance of a drug at steady state). Rifapentine and 25-desacetyl rifapentine: C_{0h} (predose plasma concentration observed on Day 1) and C_{8h} (plasma concentration observed 8 hours postdose).

Statistical Methods:

Effect of rifapentine (repeated dose) on efavirenz, emtricitabine, and tenofovir at steady state:

Pharmacokinetic parameters for efavirenz, emtricitabine, and tenofovir were summarized by using descriptive statistics for each treatment group ('ATRIPLA alone' or 'ATRIPLA + rifapentine') by day.

Treatments ratios of efavirenz, emtricitabine, and tenofovir coadministered with rifapentine (data of Day 16 on Period 2) versus administered alone (data of Day -2 of Period 1) for C_{max}, C_{min}, AUC_{0-24}, and $t_{1/2z}$ were summarized by using descriptive statistics and listed.

For log-transformed C_{max}, C_{min}, AUC_{0-24}, and $t_{1/2z}$, the effect of rifapentine (after 3 weekly administrations) on efavirenz, emtricitabine, and tenofovir was assessed using data of Day -2 (Period 1) and Day 16 (Period 2) by submitting a linear mixed effects model with fixed terms for treatment ('ATRIPLA alone' or 'ATRIPLA + rifapentine') and gender, and with an unstructured 2-by-2 matrix of treatment-specific variances and covariances for subject-within-gender block, using SAS Proc Mixed®.

For C_{max}, C_{min}, AUC_{0-24}, and $t_{1/2z}$, estimates and 90% confidence intervals (CIs) for the geometric mean ratios of efavirenz, emtricitabine, and tenofovir coadministered with rifapentine versus administered alone were obtained by computing estimates and 90% CIs for the differences between treatment means within the linear mixed effects model framework and then converting to ratios by antilog transformation.

The same model framework was used for the estimation of within-subject and total standard deviations.

Effect of rifapentine (single dose) on efavirenz, emtricitabine, and tenofovir at steady state: This analysis was performed in a similar way as described for the statistical analysis of the effect of rifapentine (after 3 weekly administrations) on efavirenz, emtricitabine, and tenofovir, but by considering data of Day -2 on Period 1 (ATRIPLA administered alone) and of Day 1 on Period 2 (ATRIPLA coadministered with rifapentine).

Safety Assessment: Adverse events (AEs), physical examination, clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), vital signs (supine and standing blood pressure, heart rate, and body temperature), 12-lead electrocardiograms (ECGs), CD4 cell counts, and viral load measurements.

RESULTS

Study Population: In total, 12 patients (10 males and 2 females) have been enrolled in Cohort 2 and have all completed the study treatment period. A summary of demographic and baseline characteristics for the study population is presented in **Table 3**.

Table 3. Demographic Characteristics

	All (N=12)
Age (years)	
Number	12
Mean (SD)	33.8 (9.1)
Min : Max	23 : 52
Sex [n (%)]	
Number	12
Male	10 (83.3%)
Female	2 (16.7%)
Race [n (%)]	
Number	12
Caucasian/White	5 (41.7%)
Black	7 (58.3%)
Weight (kg)	
Number	12
Mean (SD)	77.79 (13.30)
Min : Max	54.6 : 97.7
BMI (kg/m^2) [n (%)]	
Number	12
<30	10 (83.3%)
≥30	2 (16.7%)

For weight, baseline was assessed at P1D-2.

Pharmacokinetics:

Efavirenz PK parameters:

Emtricitabine steady state PK parameters, when administered alone, administered after a single dose of rifapentine (Period 2, Day 1), or administered 38 hours after the third weekly administration of rifapentine (Period 2, Day 16) are shown in **Table 4**. Mean (SD) efavirenz plasma concentration-time profiles, when administered alone and after a single dose of rifapentine (Period 2, Day 1), are presented in **Figure 1** (linear scale) and **Figure 2** (log-linear scale). Mean (SD) efavirenz plasma concentration-time profiles, when administered alone and 38 hours after the third weekly administration of rifapentine (Period 2, Day 16), are presented in **Figure 3** (linear scale) and **Figure 4** (log-linear scale).

Table 4. Efavirenz steady state PK parameters when administered alone, administered after a single dose of rifapentine (Period 2, Day 1), or administered after 3 weekly administrations of rifapentine (Period 2, Day 16).

Mean ± SD (Geometric mean) [CV%]	Efavirenz alone	Efavirenz + Rifapentine	
		Day 1	Day 16
C_{min}	2890 ± 2420	3000 ± 2630	2620 ± 2250
(ng/mL)	(2130) [83.6]	(2130) [87.7]	(1820) [85.8]
C_{max}	5960 ± 2830	6020 ± 2940	5500 ± 2500
(ng/mL)	(5470) [47.5]	(5510) [48.8]	(5020) [45.5]
t_{max}[a]	4.00	3.00	4.00
(h)	(1.50 - 10.00)	(1.50 - 8.00)	(2.00 - 10.00)
AUC_{0-24}	96100 ± 65600	95600 ± 68400	86600 ± 62200
(ng.h/mL)	(79900) [68.3]	(77600) [71.6]	(68600) [71.8]
$t_{1/2z}$	24.3 ± 14.6	32.3 ± 20.6	30.9 ± 20.6
(h)	(21.2) [59.9][b]	(27.2) [63.9][c]	(25.8) [66.7][d]
CL_{ss}/F	8.75 ± 4.49	9.19 ± 4.95	10.8 ± 6.70
(L/h)	(7.51) [51.3]	(7.74) [53.9]	(8.74) [62.1]

[a] Median (Min - Max)

[b] n=10, Patient 840001015, 840001019 not included in calculation of summary statistics

[c] n=11, Patient 840001023 not included in calculation of summary statistics

[d] n=10, Patient 840001015, 840001017 not included in calculation of summary statistics

Figure 1. Mean (+ SD) efavirenz plasma concentration-time profiles in linear scale when administered alone and after a single dose of rifapentine (Period 2, Day 1) (n=12)

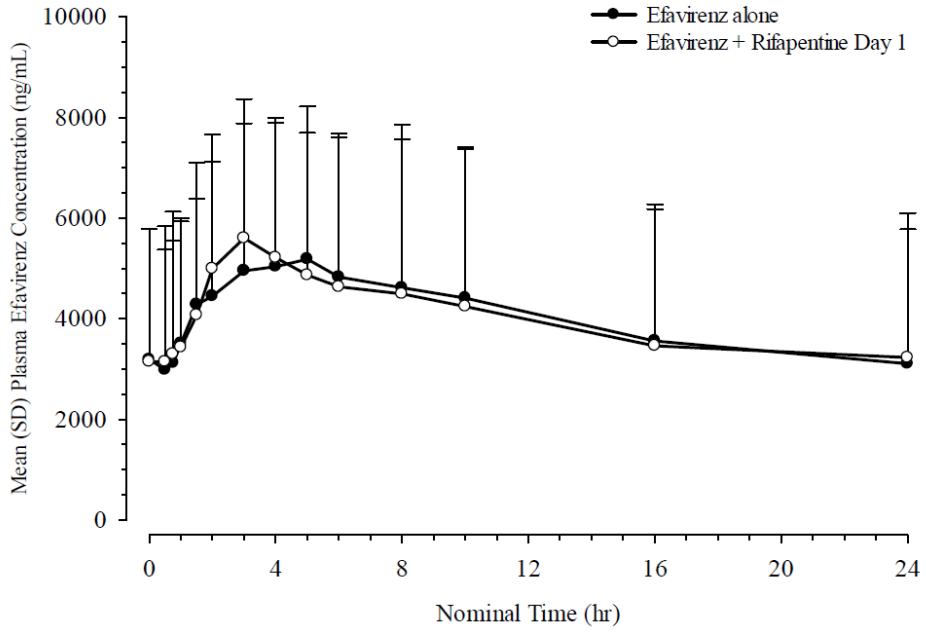


Figure 2. Mean (+ SD) efavirenz plasma concentration-time profiles in log-linear scale when administered alone and after a single dose of rifapentine (Period 2, Day 1) (n=12)

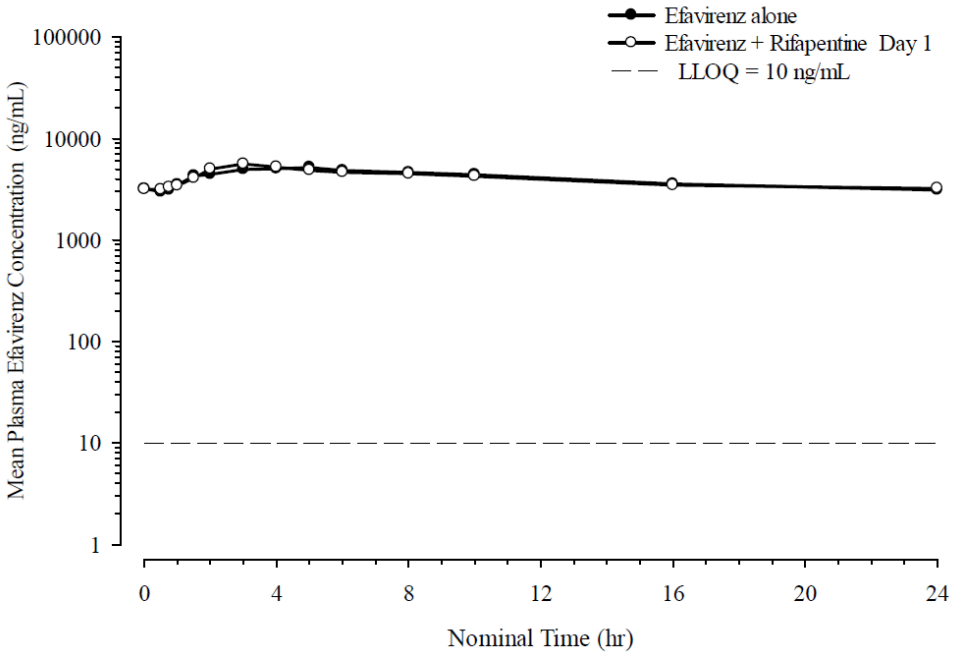


Figure 3. Mean (+ SD) efavirenz plasma concentration-time profiles in linear scale when administered alone and after repeated administrations of rifapentine (Period 2, Day 16) (n=12)

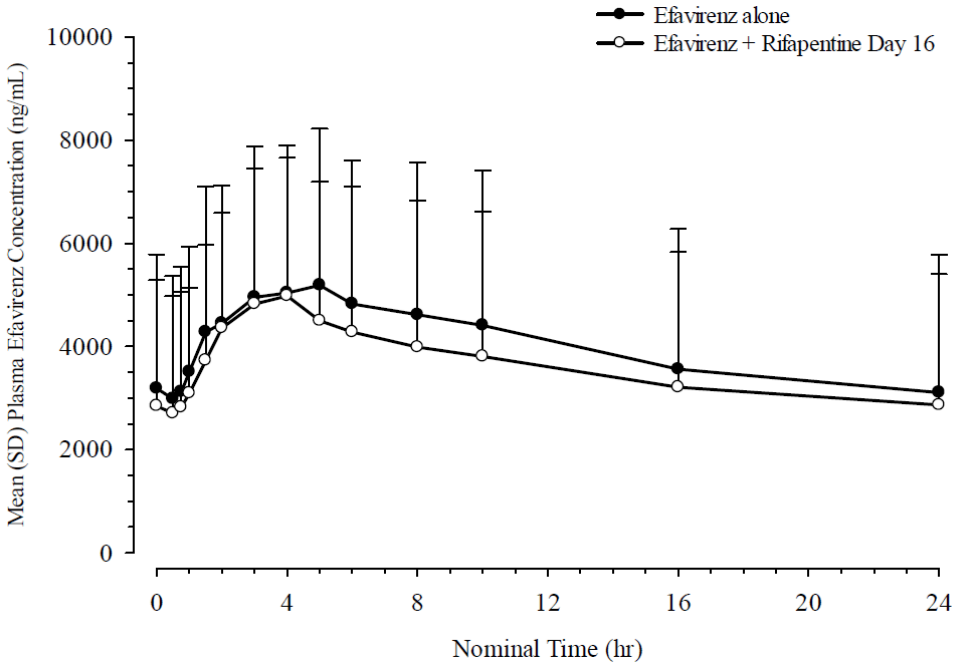
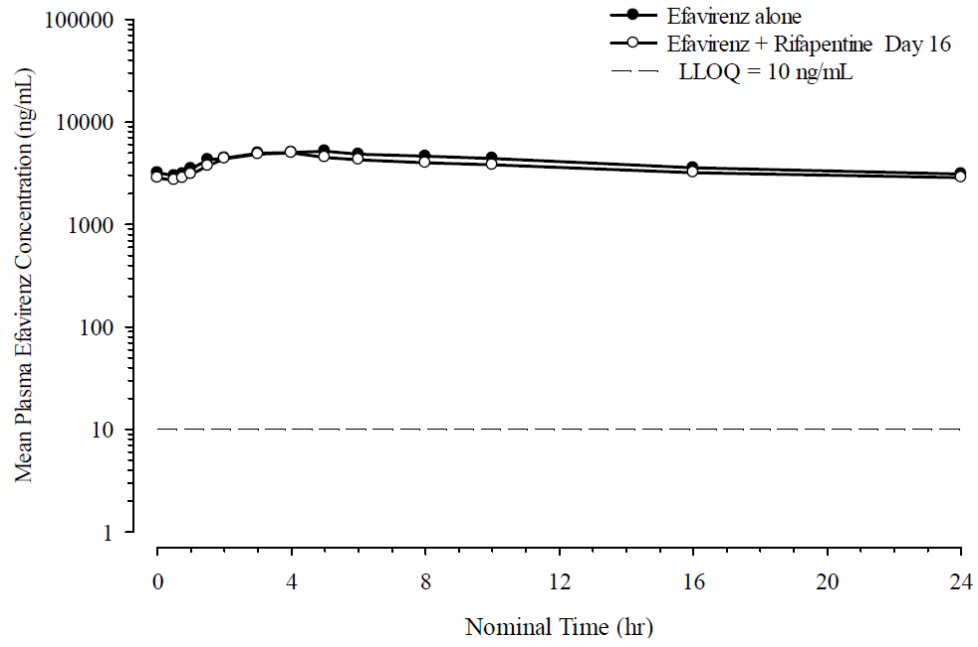


Figure 4. Mean (+ SD) efavirenz plasma concentration-time profiles in log-linear scale when administered alone and after repeated administrations of rifapentine (Period 2, Day 16) (n=12)



Effect of a single administration of rifapentine on steady state efavirenz PK
As shown in **Table 5**, efavirenz C_{min}, C_{max}, and AUC_{0-24} treatment ratio estimates are close to 1, when administered alone and after a single dose of rifapentine, indicating a lack of interaction of a single dose of rifapentine on efavirenz C_{min}, C_{max}, and AUC_{0-24} at steady state.

Table 5. Treatment ratio estimates with 90% CI for efavirenz administered after a single dose of rifapentine versus efavirenz administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Efavirenz	Atripla+rifapentine vs Atripla alone	C_{max}	1.01	(0.94 to 1.08)
		C_{min}	1.00	(0.95 to 1.05)
		AUC_{0-24}	0.97	(0.93 to 1.01)

Effect of repeated administrations of rifapentine on steady state efavirenz PK
As shown in **Table 6,** treatment ratio estimates indicated a decrease in efavirenz C_{min} and AUC_{0-24} of around 15% after repeated doses of rifapentine, while efavirenz C_{max} at steady state was not affected by repeated doses of rifapentine.

Table 6. Treatment ratio estimates with 90% CI for efavirenz administered after repeated doses of rifapentine versus efavirenz administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Efavirenz	Atripla+rifapentine vs Atripla alone	C_{max}	0.92	(0.82 to 1.03)
		C_{min}	0.85	(0.79 to 0.93)
		AUC_{0-24}	0.86	(0.79 to 0.93)

Efavirenz median T_{max} was not modified by single or repeated administrations of rifapentine.

Reviewer Comments: *In vitro (Study IHH0013), rifapentine and the metabolite, 25-desacetyl-rifapentine, induce CYP3A4 and CYP2B6 gene expression and activities. For CYP3A4, E_{max} (maximal fold increase of mRNA expression) were estimated as 29-fold and 22-fold, for rifapentine and 25-desacetyl-rifapentine, respectively; EC_{50} (concentration resulting in half-maximal induction) was about 3 µM for both compounds. For CYP2B6, EC50s were estimated as 3.60 µM and 11.7 µM for rifapentine and 25-desacetyl-rifapentine, respectively, and Emax was around 4-fold for both compounds. In vivo (Study INT12291), co-administration of weekly doses of rifapentine caused a moderate decrease (~15%) in C_{min} and AUC of efavirenz, which is not considered to be clinically significant (this conclusion has been confirmed by Antiviral colleagues). Efavirenz is a probe substrate of CYP2B6; the lack of significant changes in efavirenz PK observed in this clinical study indicates the drug-drug interaction potential of weekly dosing of rifapentine with CYP2B6 substrates appears to be low.*

Emtricitabine PK Parameters

Emtricitabine steady state PK parameters when administered alone, administered after a single dose of rifapentine (Period 2, Day 1), or administered after 3 weekly administrations of rifapentine (Period 2, Day 16) are shown in **Table 7**. Mean (SD) emtricitabine plasma concentration-time profiles, when administered alone and after a single dose of rifapentine (Period 2, Day 1), are presented in **Figure 5** (linear scale) and **Figure 6** (log-linear scale). Mean (SD) emtricitabine plasma concentration-time profiles, when administered alone and 38 hours after the third weekly administration of rifapentine (Period 2, Day 16), are presented in **Figure 7** (linear scale) and **Figure 8** (log-linear scale).

Table 7. Emtricitabine steady state PK parameters when administered alone, administered after a single dose of rifapentine (Period 2, Day 1), or administered after 3 weekly administrations of rifapentine (Period 2, Day 16)

Mean ± SD (Geometric mean) [CV%]	Emtricitabine alone	Emtricitabine + Rifapentine	
		Day 1	Day 16
C_{min}	52.6 ± 11.6	56.1 ± 12.9	51.7 ± 14.8
(ng/mL)	(51.4) [22.1]	(54.8) [22.9]	(50.0) [28.6]
C_{max}	1620 ± 357	1660 ± 318	1540 ± 371
(ng/mL)	(1580) [22.1]	(1630) [19.2]	(1490) [24.2]
t_{max}[a]	2.00	2.00	2.00
(h)	(1.00 - 6.00)	(0.75 - 4.00)	(1.00 - 4.00)
AUC_{0-24}	9440 ± 1160	9130 ± 1430	8860 ± 1570
(ng.h/mL)	(9370) [12.3]	(9030) [15.7]	(8740) [17.8]
$t_{1/2z}$	5.88 ± 1.08	6.49 ± 1.01	6.14 ± 1.34
(h)	(5.79) [18.4]	(6.42) [15.6]	(6.02) [21.8]
CLss/F	21.5 ± 2.70	22.4 ± 3.51	23.2 ± 4.12
(L/h)	(21.3) [12.6]	(22.2) [15.6]	(22.9) [17.7]

[a] Median (Min - Max)

Figure 5. Mean (+ SD) emtricitabine plasma concentration-time profiles in linear scale when administered alone and after a single dose of rifapentine (Period 2, Day 1) (n=12)

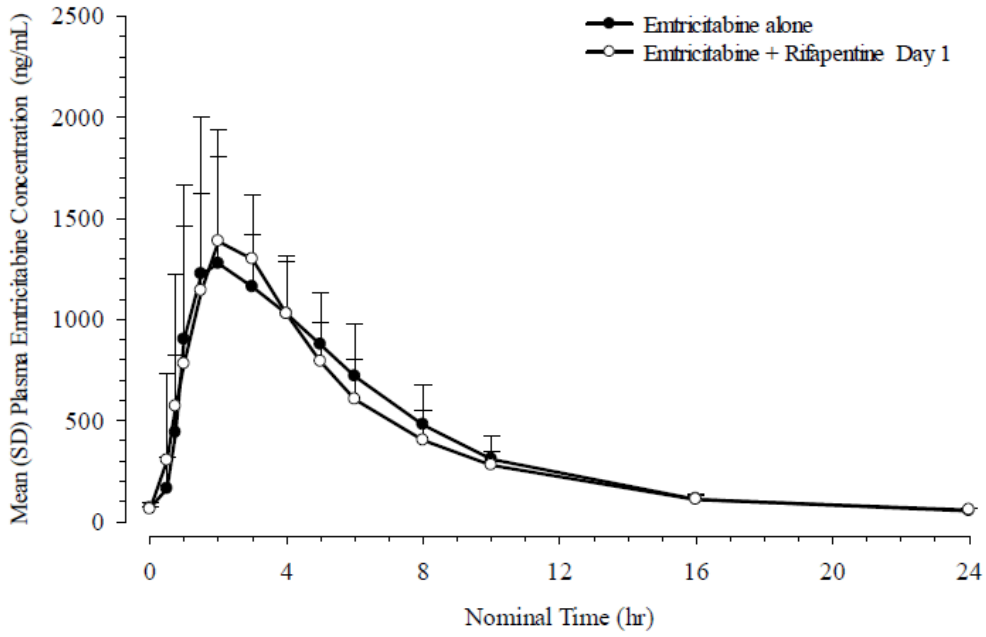


Figure 6. Mean (+ SD) emtricitabine plasma concentration-time profiles in log-linear scale when administered alone and after a single dose of rifapentine (Period 2, Day 1) (n=12)

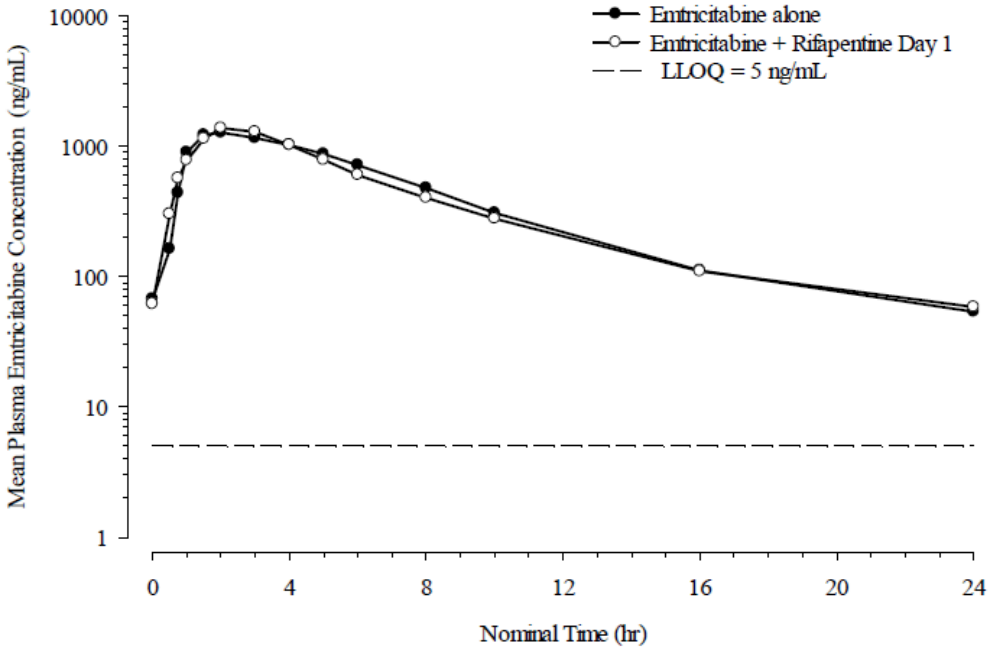


Figure 7. Mean (+ SD) emtricitabine plasma concentration-time profiles in linear scale when administered alone and after repeated doses of rifapentine (Period 2, Day 16) (n=12)

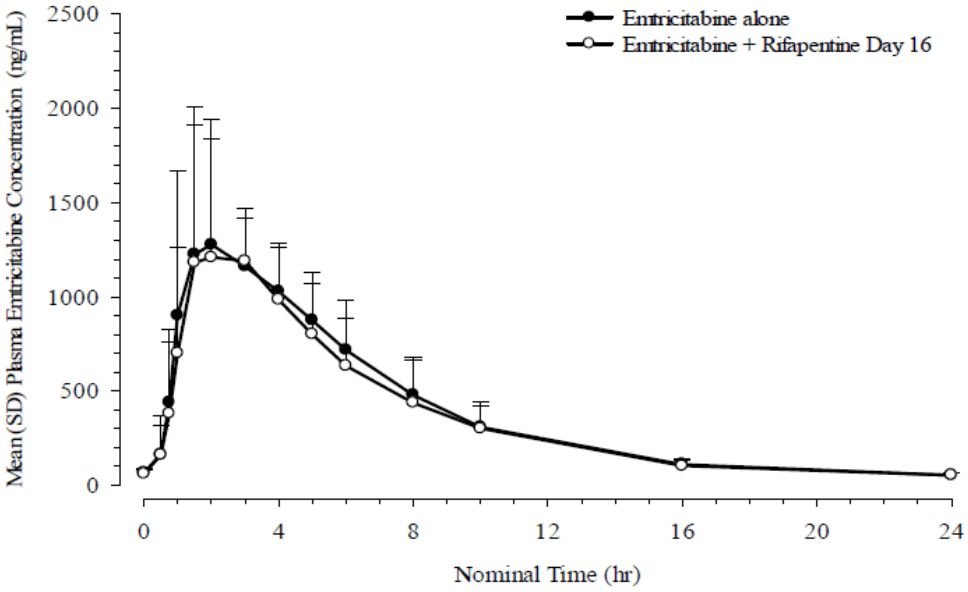
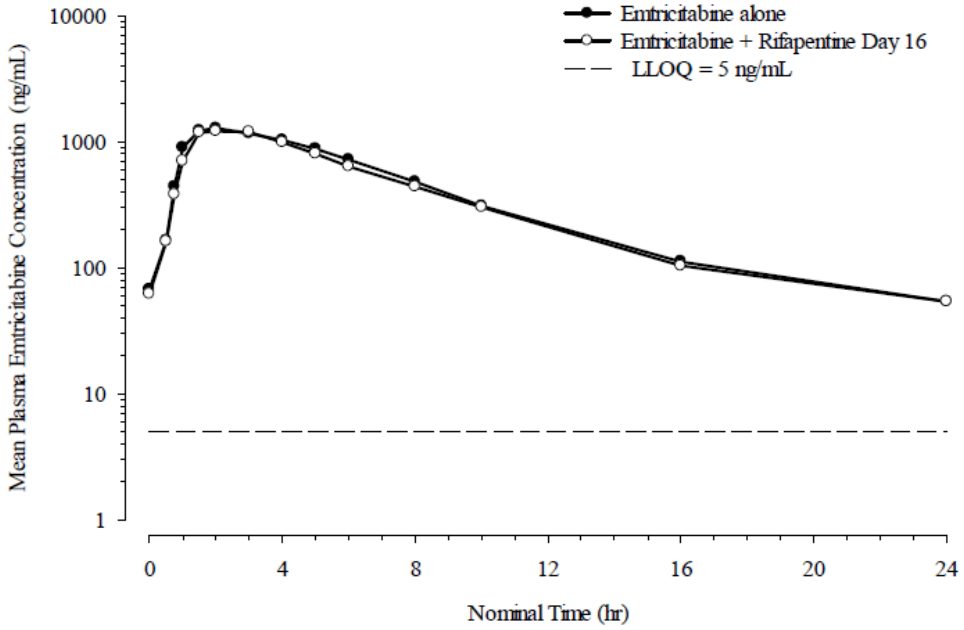


Figure 8. Mean (+ SD) emtricitabine plasma concentration-time profiles in log-linear scale when administered alone and after repeated doses of rifapentine (Period 2, Day 1) (n=12)



Effect of a single administration of rifapentine on steady state emtricitabine PK

As shown in **Table 8**, emtricitabine C_{min}, C_{max}, and AUC_{0-24} treatment ratio estimates were close to 1, when administered alone and after a single dose of rifapentine, indicating a lack of effect of a single dose of rifapentine on emtricitabine C_{min}, C_{max}, and AUC_{0-24} at steady state.

Table 8. Treatment ratio estimates with 90% CI for emtricitabine administered after a single dose of rifapentine versus emtricitabine administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Emtricitabine	Atripla+rifapentine vs Atripla alone	C_{max}	1.03	(0.93 to 1.14)
		C_{min}	1.07	(0.99 to 1.15)
		AUC_{0-24}	0.96	(0.92 to 1.01)

Effect of repeated administrations of rifapentine on steady state emtricitabine PK
As shown in **Table 9**, emtricitabine C_{min}, C_{max}, and AUC_{0-24} treatment ratio estimates were close to 1, when administered alone and after a single dose of rifapentine, indicating a lack of effect of repeated doses of rifapentine on emtricitabine C_{min}, C_{max}, and AUC_{0-24} at steady state.

Table 9. Treatment ratio estimates with 90% CI for emtricitabine administered after repeated doses of rifapentine versus emtricitabine administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Emtricitabine	Atripla+rifapentine vs Atripla alone	C_{max}	0.95	(0.81 to 1.10)
		C_{min}	0.97	(0.90 to 1.05)
		AUC_{0-24}	0.93	(0.89 to 0.98)

Emtricitabine median t_{max} was not modified by single or repeated administrations of rifapentine.

Reviewer Comment: *Emtricitabine is predominately excreted in urine via glomerular filtration and active tubular secretion with limited metabolism, which explains the lack of drug-drug interaction effect of rifapentine on emtricitabine observed in this clinical study.*

Tenofovir PK Parameters

Tenofovir steady state PK parameters when administered alone, administered after a single dose of rifapentine (Period 2, Day 1), or administered after 3 weekly administrations of rifapentine (Period 2, Day 16) are shown in **Table 10**. Mean (SD) tenofovir plasma concentration-time profiles, when administered alone and after a single dose of rifapentine (Period 2, Day 1), are presented in **Figure 9** (linear scale) and **Figure 10** (log-linear scale). Mean (SD) tenofovir plasma concentration-time profiles, when administered alone and 38 hours after the third weekly administration of rifapentine (Period 2, Day 16), are presented in **Figure 11** (linear scale) and **Figure 12** (log-linear scale).

Table 10. Tenofovir steady state PK parameters when administered alone, administered after a single dose of rifapentine (Period 2, Day 1), or administered after 3 weekly administrations of rifapentine (Period 2, Day 16)

Mean ± SD (Geometric mean) [CV%]	Tenofovir alone	Tenofovir + Rifapentine	
		Day 1	Day 16
C_{min}	49.7 ± 8.40	46.6 ± 9.18	45.3 ± 15.0
(ng/mL)	(49.1) [16.9]	(45.8) [19.7]	(42.9) [33.1]
C_{max}	278 ± 85.3	347 ± 135	277 ± 81.9
(ng/mL)	(266) [30.7]	(326) [39.0]	(266) [29.5]
t_{max}[a]	1.75	1.75	2.00
(h)	(1.00 - 5.00)	(0.50 - 4.00)	(1.00 - 4.00)
AUC_{0-24}	2260 ± 310	2370 ± 652	2090 ± 423
(ng.h/mL)	(2240) [13.7]	(2290) [27.5]	(2050) [20.3]
$t_{1/2z}$	21.0 ± 6.99	19.2 ± 4.70	19.0 ± 4.44
(h)	(20.1) [33.2]	(18.8) [24.4]	(18.5) [23.3]
CLss/F	61.1 ± 9.09	61.1 ± 15.5	67.6 ± 14.3
(L/h)	(60.5) [14.9]	(59.2) [25.3]	(66.3) [21.2]

[a] Median (Min - Max)

Figure 9. Mean (+ SD) tenofovir plasma concentration-time profiles in linear scale when administered alone and after a single dose of rifapentine (Period 2, Day 1) (n=12)

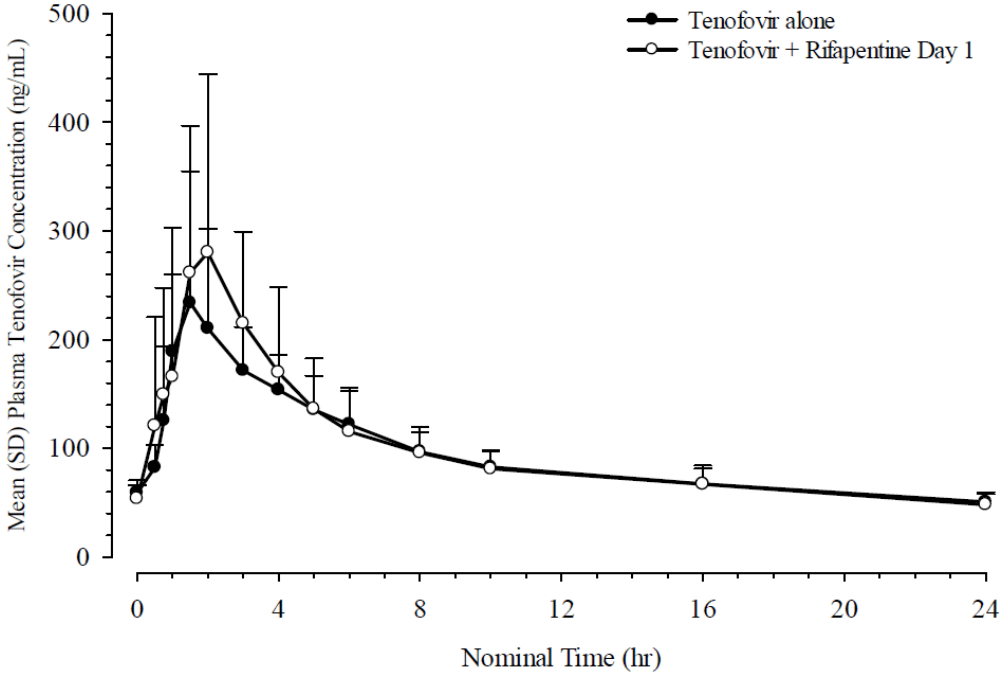


Figure 10. Mean (+ SD) tenofovir plasma concentration-time profiles in log-linear scale when administered alone and after a single dose of rifapentine (Period 2, Day 1) (n=12)

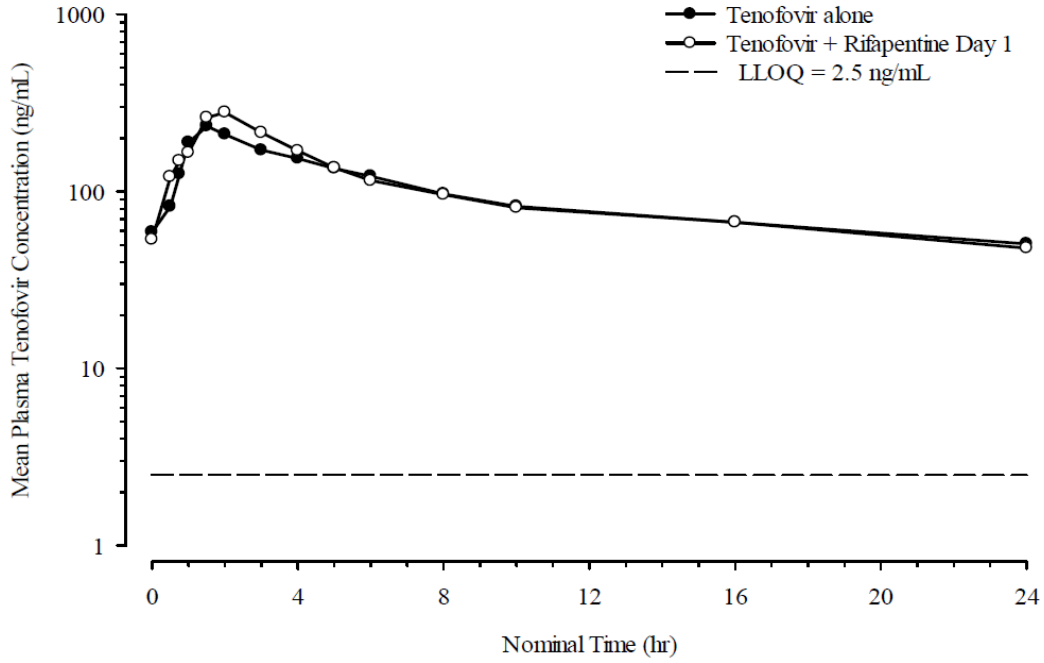


Figure 11. Mean (+ SD) tenofovir plasma concentration-time profiles in linear scale when administered alone and after repeated doses of rifapentine (Period 2, Day 16) (n=12)

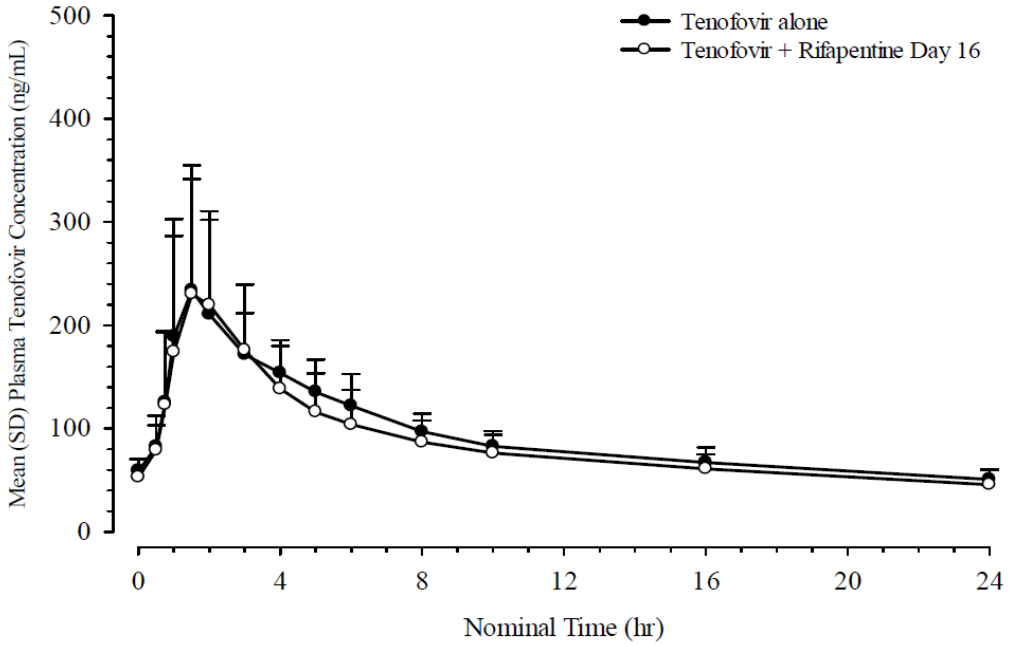
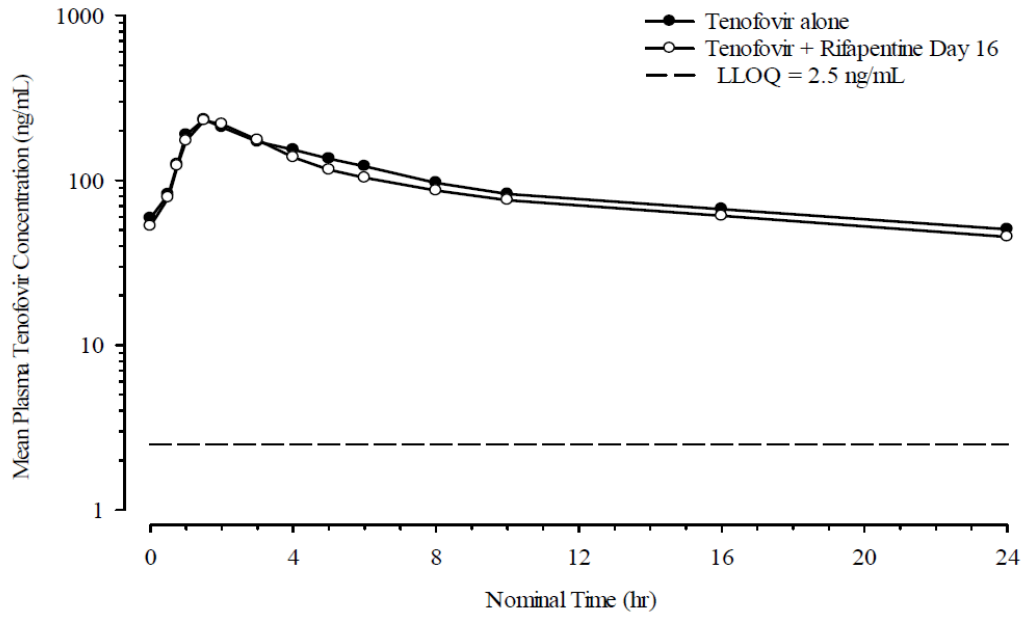


Figure 12. Mean (+ SD) tenofovir plasma concentration-time profiles in log-linear scale when administered alone and after repeated doses of rifapentine (Period 2, Day 16) (n=12)



Effect of a single administration of rifapentine on steady state tenofovir PK
As shown in **Table 11**, tenofovir C_{max} increased by 23% after co-administration with a single dose of rifapentine; whereas, tenofovir C_{min} and AUC_{0-24} were not affected.

Table 11. Treatment ratio estimates with 90% CI for tenofovir administered after a single dose of rifapentine versus tenofovir administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Tenofovir	Atripla+rifapentine vs Atripla alone	C_{max}	1.23	(1.00 to 1.51)
		C_{min}	0.93	(0.84 to 1.03)
		AUC_{0-24}	1.02	(0.91 to 1.15)

Reviewer Comment: *The transient increase in tenofavir C_{max} (by 23%) after co-administered with a single dose of rifapentine is not considered to be clinically relevant.*

Effect of repeated administrations of rifapentine on steady state tenofovir PK
As shown in **Table 12**, tenofovir C_{max} and AUC_{0-24} treatment ratio estimates were close to 1, indicating that C_{max} and AUC_{0-24} are not affected after repeated administrations of rifapentine. However, tenofovir C_{min} was 13% lower when co-administered with weekly dosing of rifapentine.

Table 12. Treatment ratio estimates with 90% CI for tenofovir administered after repeated administrations of rifapentine versus tenofovir administered alone

Compound	Comparison	Parameter	Estimate	90% CI
Tenofovir	Atripla+rifapentine vs Atripla alone	C_{max}	1.00	(0.82 to 1.22)
		C_{min}	0.87	(0.73 to 1.05)
		AUC_{0-24}	0.91	(0.85 to 0.98)

Reviewer Comment: *Tenofovir is not a substrate of CYP enzymes. Following IV administration of tenofovir, approximately 70–80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. The moderate decrease in tenofavir C_{min} (by 13%) after co-administered with weekly dosing of rifapentine is not considered to be clinically significant (this conclusion has been confirmed with Antiviral colleagues).*

Rifapentine Pharmacokinetics
Mean (CV%) rifapentine and the metabolite, 25-DR, plasma concentrations observed after weekly administrations of rifapentine, in Period 2 on Day 1, Day 8 and Day 15, are presented in **Table 13**.

Table 13. Mean (CV%) rifapentine and 25-DR plasma concentrations

	Mean (CV%) concentration (µg/mL) over Nominal Time (hr)					
	Day 1	Day 1	Day 1	Day 8	Day 15	Day 15
	Pre-dose	8.00	24.00	8.00	8.00	48.00
Plasma RIFAPENTINE	<LLOQ (NA)	14.0 (20.6)	6.87 (44.3)	14.3 (19.2)	15.4 (21.0)	1.13 (199.1)
Plasma 25-DR	<LLOQ (NA)	5.34 (27.8)	5.46 (47.1)	6.04 (16.7)	6.45 (38.9)	<LLOQ (NC)

<LLOQ = Below the lower limit of quantification (1 µg/mL)
NA = not applicable
NC = not calculated

Reviewer Comment: *This study was not designed to evaluate the effect of the components of Atripla on rifapentine. Nevertheless, using inter-study comparison of plasma concentrations (24h post dose) from INT12291 and TBTC 26 PK studies, mean concentrations of RPT (6.9 µg/mL versus 8.5 µg/mL) and 25-DR (5.5 µg/mL versus 10.4 µg/mL) were lower in HIV-infected patients taking Atripla compared to those observed in LTBI adult patients in TBTC-S26 PK sub study. However, further investigations are warranted to confirm these observations.*

Safety: There were no serious AEs or severe TEAEs reported during the study course. All TEAEs were of mild intensity and were reported in majority during the coadministration of ATRIPLA with rifapentine (11 out of 12 patients) as compared to ATRIPLA alone (3 out of 12 patients).

Renal and urinary disorders (chromaturia) and nervous system disorders (mainly headache and somnolence) were the most frequent system-organ class affected during the coadministration period (10 out of 12 patients [83%] and 5 out of 12 patients [42%], respectively).

Few isolated and no clinically relevant PCSAs have been reported for laboratory parameters, vital signs, and ECGs. Of note, 1 patient (No. 840001019) presented PCSA values for platelet count (minimum value of 55 Giga/L) with an already low value at screening (57 Giga/L) and 1 patient (No. 840001021) who had an elevated baseline triglycerides value (7.06 mmol/L) presented a PCSA for triglycerides (maximum value of 14.11 mmol/L).

No clinically significant modification was reported throughout the study on the CD4 cell counts and the viral loads in any of the patients as compared to baseline.

SPONSOR'S CONCLUSIONS
Coadministration of ATRIPLA (the fixed dose combination of efavirenz, emtricitabine, and tenofovir) with a single 900 mg dose of rifapentine did not result in any change in steady state exposure (C_{min}, C_{max}, and AUC_{0-24}) for efavirenz and emtricitabine compared to ATRIPLA administered alone. Regarding tenofovir, the coadministration of ATRIPLA with a single dose of rifapentine led to an increase of 23% in C_{max} without any change in C_{min} and AUC_{0-24}.

ATRIPLA PK was evaluated 38 hours after the third weekly administration of rifapentine which is considered to be the time course for maximal CYP3A4 and CYP2B6 induction. After the third

weekly 900 mg administrations of rifapentine, the efavirenz, emtricitabine, and tenofovir steady state exposure (C_{min}, C_{max}, and AUC_{0-24}) was generally comparable to ATRIPLA administered alone, with small decreases observed in some PK parameters: efavirenz C_{min} and AUC_{0-24} were decreased by 15% and 14%, respectively, and tenofovir C_{min} was decreased by 13%.

Overall, the coadministration of ATRIPLA with weekly rifapentine was well tolerated. The majority of AEs reported were of mild intensity. No unexpected clinically significant AEs or laboratory abnormalities were observed in this study. In addition, no clinically significant modifications of CD4 cell counts or viral loads were observed.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results. Although co-administration of ATRIPLA and rifapentine caused a moderate decrease in efavirenz C_{min} and AUC_{0-24} (by ~15%) and tenofovir C_{min} (by 13%), this level of changes is not considered to be clinically significant; therefore, no dose adjustment is needed in patients co-administered with once daily dosing of ATRIPLA and weekly dosing of rifapentine.

STUDY NO.: INT12099

An open-label, randomized, four-period, four-sequence, four-treatment crossover pharmacokinetic interaction study of a single oral dose of 900 mg rifapentine and a single oral dose of 900 mg isoniazid in healthy male and female subjects

Date(s): 27 May 2011to 28 July 2011
Sponsor: SANOFI AVENTIS US LLC

OBJECTIVE(S):

Primary objectives

- To assess the effect of a co-administration of single oral dose of rifapentine and isoniazid on the pharmacokinetics of rifapentine and isoniazid, in fasting conditions
- To assess the food effect on the pharmacokinetics of rifapentine and isoniazid when the single oral dose of rifapentine and isoniazid are co-administered

Secondary objectives

- To assess the effect of a co-administration of single oral dose of rifapentine and isoniazid on the pharmacokinetics of 25-desacetyl-rifapentine, in fasting conditions
- To assess the food effect on the pharmacokinetics of 25-desacetyl-rifapentine when the single oral dose of rifapentine and isoniazid are co-administered
- To assess the clinical and laboratory safety of rifapentine co-administered with isoniazid.

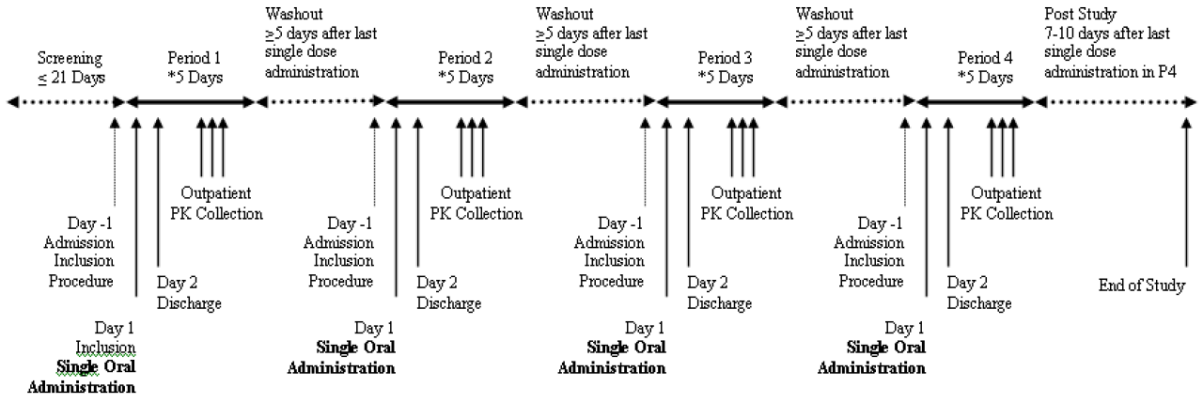
METHODS

Study Design: This was a single dose, open-label, randomized, four-sequence, four-period, four-treatment, cross-over study. Four treatment groups were investigated in this single-center Phase 1 study:

- Treatment A: single dose of 900 mg rifapentine (fasted conditions)
- Treatment B: single dose of 900 mg isoniazid (fasted conditions)
- Treatment C: single dose of 900 mg rifapentine + 900 mg isoniazid (fasted conditions)
- Treatment D: single dose of 900 mg rifapentine + 900 mg isoniazid (fed conditions: low fat, high carbohydrate breakfast)

The total wash-out period between two administrations lasted at least 5 days following the single oral administration. A summary of the study design is provided in **Figure 1** below.

Figure 1. Study design.



* Isoniazid only treatment period is 4 days

Study Treatment:

Rifapentine

Formulation:

• Tablet (150 mg of active substance) administered under fasted conditions for Treatments A and C;

• Tablet administered under fed conditions for Treatment D

Route(s) of administration: oral route at 8:00 am with 350 mL of non-carbonated water

Dose regimen: 900 mg per administration

Batch number(s): C1014802 / 1A0009

Isoniazid

Formulation:

• Tablet (300 mg of active substance) administered under fasted conditions for Treatments B and C;

• Tablet (300 mg of active substance) administered under fed conditions for Treatment D.

Route(s) of administration: oral route at 8:00 am with 350 mL of non-carbonated water

Dose regimen: 900 mg per administration

Batch number(s): ME090963

Inclusion/Exclusion Criteria: Male or non-pregnant, non-nursing female healthy subjects (at least 30% of each gender was to be enrolled), aged between 18 and 55 years inclusive, body weight between 50 kg and 95 kg if males, between 50 kg and 85 kg if females, Body Mass Index (BMI) between 18 and 30 kg/m^2, were enrolled.

Any medication (including St John's Wort and aspirin) were prohibited within 14 days before inclusion, or within 5 times the elimination half-life of that drug, whichever the longest with the exception of hormonal contraception.

PK Sample Collection:

Blood samples were collected at predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 16, and 24, 36, 48, and 72 hours postdose (this last sample was only drawn for rifapentine and 25-desacetyl-rifapentine assays).

Analytical Methods:
Rifapentine/25-desacetyl metabolite and isoniazid concentrations were analyzed using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods (**Table 1**).

Table 1. Bioanalytical results of rifapentine, 25-desacetyl rifapentine, and isoniazid in plasma

Criterion	Rifapentine	25-desacetyl Rifapentine	Isoniazid	Comments
Calibration Range	0.05-10 µg/mL	0.05-10 µg/mL	0.05-15 µg/mL	Satisfactory
LLOQ	50 ng/mL	50 ng/mL	50 ng/mL	Satisfactory
Linearity, mean R^2	≥0.9908	≥0.9918	≥0.9925	Satisfactory
Accuracy	Within ±2.5%	Within ±2.0%	Within ±3.6%	Satisfactory
Precision, CV	≤ 7.2%	≤ 5.8%	≤5.4%	Satisfactory
Quality Control	0.15, 5.00, 8.00 µg/mL	0.15, 5.00, 8.00 µg/mL	0.15, 7.5, 12.0 µg/mL	Satisfactory
Accuracy	Within ± 6.0%	Within ± 4.0%	Within ±9.3%	Satisfactory
Precision, CV	≤ 7.4%	≤ 7.2%	≤8.5%	Satisfactory
Stability	• Rifapentine and 25-desacetyl rifapentine are stable in matrix for at least 24 hours at room temperature or +4°C, after three additional freeze/thaw cycles at -20°C or -80°C, after at least 110 days at -20°C or -80°C for rifapentine. For 25-desacetyl rifapentine long term stability in matrix is demonstrated within the range of the calibration curve for at least 110 days at -20°C or -80°C. Diluted samples out of range up to 100 µg/mL are stable for up to 44 days at -20°C or -80°C. Diluted samples out of range up to 25 µg/mL are stable for up to 69 days at -20°C or -80°C. Rifapentine and 25-desacetyl rifapentine are also stable in extract for at least 96 hours at +5°C. 25-desacetyl rifapentine is stable in blood at +4°C for at least 4 hours. Rifapentine is stable in blood at +4°C for up to 2 hours only. • The overall storage period of 58 days until analysis is covered by the available stability data			Satisfactory

Pharmacokinetic Assessment:
- C_{max}, T_{max}, T_{lag}, AUC_{last}, AUC and $t_{1/2z}$ were calculated for rifapentine, 25-desacetyl-rifapentine and isoniazid
- Vss/F and CL/F were also calculated for both rifapentine and isoniazid

Safety Assessment: Adverse events (AEs), clinical laboratory tests (hematology, biochemistry and urinalysis), vital signs, and automatic reading electrocardiograms (ECGs).

RESULTS
Study Population: A total of 17 subjects were treated with isoniazid and/or rifapentine during this study and included in the safety and PK populations. A summary of demographic and baseline characteristics for the study population is presented in **Table 2**.

Table 2. Demographic Characteristics

	All (N=17)
Age (years)	
Number	17
Mean (SD)	34.3 (10.9)
Median	33.0
Min : Max	19 : 55
Sex [n (%)]	
Number	17
Male	11 (64.7%)
Female	6 (35.3%)
Race [n (%)]	
Number	17
Caucasian/White	9 (52.9%)
Black	6 (35.3%)
Other	2 (11.8%)
Weight (kg)	
Number	17
Mean (SD)	77.12 (8.47)
Median	73.40
Min : Max	65.8 : 91.0
BMI (kg/m^2)	
Number	17
Mean (SD)	26.07 (2.32)
Median	26.45
Min : Max	20.7 : 29.4

Pharmacokinetics:

Plasma Concentrations

Mean (SD) plasma rifapentine and 25-desacetyl-rifapentine concentrations versus time following a single dose of rifapentine (900 mg) administered alone in fasted condition or co-administered with isoniazid in fasted or fed conditions are presented in **Figure 2** and **Figure 3,** respectively. Mean (SD) plasma isoniazid concentrations versus time following a single oral administration of isoniazid (900 mg) administered alone in fasted condition or co-administered with rifapentine in fasted or fed conditions are presented in **Figure 4**.

Figure 2 - Mean (SD) plasma rifapentine concentrations versus time following a single oral administration of rifapentine (900 mg) administered alone in fasted condition or co-administered with isoniazid in fasted or fed conditions in linear (left) and semi-log (right) scale

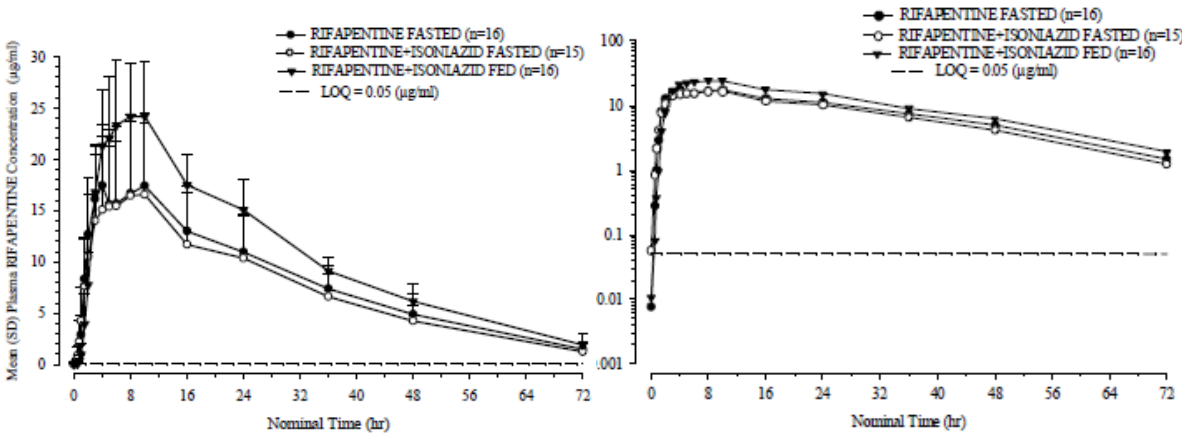


Figure 3 - Mean (SD) plasma 25-desacetyl-rifapentine concentrations versus time following a single oral administration of rifapentine (900 mg) administered alone in fasted condition or coadministered with isoniazid in fasted or fed conditions in linear (left) and semi-log (right) scale

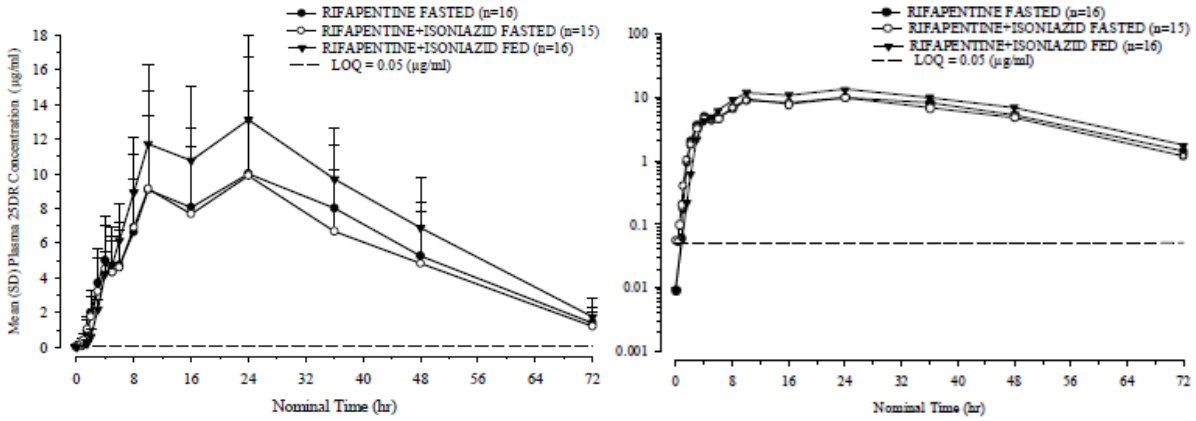
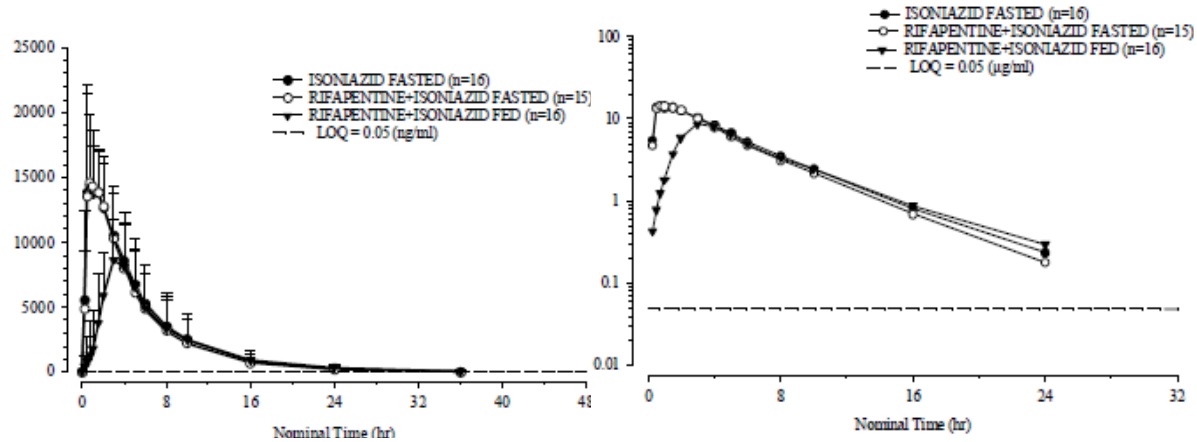


Figure 4 - Mean (SD) plasma isoniazid concentrations versus time following a single oral administration of isoniazid (900 mg) administered alone in fasted condition or co-administered with rifapentine in fasted or fed conditions in linear (left) and semi-log (right) scale



Descriptive statistics on PK parameters:
Descriptive statistics on PK parameters of Rifapentine, 25-desacetyl-rifapentine, and isoniazid are summarized in **Tables 3, 4**, and **5**, respectively.

Table 3. Rifapentine PK parameters administered alone in fasted condition or co-administered with isoniazid in fasted or fed conditions

Mean ± SD (Geometric Mean) [CV%]	Plasma RIFAPENTINE		
	RIFAPENTINE FASTED	RIFAPENTINE+ISONIAZID FASTED	RIFAPENTINE+ISONIAZID FED
N	16	15	16
C_{max}	19.5 ± 6.92	18.7 ± 8.21	25.8 ± 5.83
(µg/ml)	(18.4) [35.4]	(16.9) [43.9]	(25.2) [22.6]
t_{max}[a]	4.00	4.00	8.00
(hr)	(2.00 - 10.00)	(2.00 - 10.02)	(3.00 - 10.00)
t_{lag}[a]	0.25	0.25	0.50
(hr)	(0.00 - 0.75)	(0.00 - 0.75)	(0.00 - 1.00)
$t_{1/2z}$	16.8 ± 3.70	16.1 ± 4.18	16.6 ± 5.02
(hr)	(16.4) [22.0]	(15.6) [26.0]	(15.9) [30.2]
AUC_{last}	585 ± 190	537 ± 195	764 ± 109
(µg•hr/ml)	(560) [32.5]	(500) [36.4]	(757) [14.3]
AUC	624 ± 204	570 ± 207	817 ± 128
(µg•hr/ml)	(597) [32.7]	(530) [36.4]	(808) [15.7]
V_{ss}/F	44.7 ± 15.2	50.6 ± 22.5	32.0 ± 6.33
(L)	(42.5) [34.1]	(46.4) [44.6]	(31.4) [19.8]
CL/F	1.57 ± 0.421	1.85 ± 0.872	1.13 ± 0.174
(L/hr)	(1.51) [26.9]	(1.70) [47.1]	(1.11) [15.4]

[a] Median (Min - Max)

NA = Not Applicable

Table 4. 25-desacetyl-rifapentine PK parameters when rifapentine administered alone in fasted condition or co-administered with isoniazid in fasted or fed conditions

Mean ± SD (Geometric Mean) [CV%]	Plasma 25-DESACETYL RIFAPENTINE		
	RIFAPENTINE FASTED	RIFAPENTINE+ISONIAZID FASTED	RIFAPENTINE+ISONIAZID FED
N	16	15	16
C_{max}	10.3 ± 4.68	10.2 ± 6.74	13.3 ± 4.83
(µg/ml)	(9.40) [45.6]	(8.32) [66.0]	(12.5) [36.5]
t_{max}[a]	24.00	24.00	24.00
(hr)	(10.00 - 36.00)	(10.00 - 24.02)	(10.00 - 36.00)
$t_{1/2z}$	16.6 ± 4.78	16.7 ± 5.08	17.5 ± 7.42
(hr)	(16.0) [28.7]	(16.1) [30.4]	(16.3) [42.3]
AUC_{last}	436 ± 196	406 ± 239	554 ± 169
(µg•hr/ml)	(402) [44.9]	(343) [58.9]	(532) [30.6]
AUC	474 ± 212	443 ± 262	601 ± 187
(µg•hr/ml)	(436) [44.8]	(372) [59.1][b]	(578) [31.0][c]

[a] Median (Min - Max)

[b] n=14, Subject 840001001 not included in calculation of summary statistics

[c] n=15, Subject 840001007 not included in calculation of summary statistics

NA = Not Applicable

Table 5. Isoniazid PK parameters administered alone in fasted condition or co-administered with rifapentine in fasted or fed conditions

Mean ± SD (Geometric Mean) [CV%]	Plasma ISONIAZID		
	ISONIAZID FASTED	RIFAPENTINE+ISONIAZID FASTED	RIFAPENTINE+ISONIAZID FED
N	16	15	16
C_{max}	19.0 ± 4.83	18.3 ± 6.65	9.60 ± 2.73
(µg/mL)	(18.4) [25.5]	(17.2) [36.3]	(9.28) [28.5]
t_{max}[a]	0.75	0.75	3.00
(hr)	(0.25 - 2.00)	(0.50 - 2.00)	(0.75 - 5.00)
t_{lag}[a]	0.00	0.00	0.00
(hr)	(0.00 - 0.00)	(0.00 - 0.00)	(0.00 - 0.25)
$t_{1/2z}$	3.14 ± 1.18	3.08 ± 1.09	3.87 ± 1.06
(hr)	(2.92) [37.7]	(2.90) [35.3]	(3.72) [27.5]
AUC_{last}	88.2 ± 39.2	83.0 ± 37.0	63.7 ± 34.2
(µg•hr/ml)	(79.6) [44.5]	(75.3) [44.5]	(55.7) [53.8]
AUC	88.9 ± 39.5	83.7 ± 37.2	64.3 ± 34.4
(µg•hr/ml)	(80.2) [44.5]	(75.9) [44.4]	(56.4) [53.5]
CL/F	12.5 ± 6.25	13.1 ± 6.02	18.0 ± 8.53
(L/hr)	(11.2) [49.9]	(11.9) [46.0]	(16.0) [47.4]
V_{ss}/F	52.5 ± 11.2	53.7 ± 13.0	109 ± 39.5
(L)	(51.4) [21.3]	(52.3) [24.2]	(103) [36.2]

[a] Median (Min - Max)
NA = Not Applicable

Rifapentine-isoniazid interactions
As shown in **Table 6**, the ratio estimates for rifapentine C_{max}, AUC_{last} and AUC (rifapentine with isoniazid versus rifapentine alone) were within the protocol-specified range [0.8 - 1.25] but the lower limit of the confidence interval was just below 0.8. When rifapentine was administered with isoniazid, rifapentine C_{max} and AUCs were decreased by 6% and 9%, respectively, compared when administered alone. Based on the 90% CI of $t_{1/2z}$, rifapentine $t_{1/2z}$ was not different when rifapentine was administered alone or with isoniazid.

Reviewer Comment: *The changes in rifapentine C_{max} and AUC (6 and 9%, respectively) when co-administered with isoniazid were less than the inter-individual variability of rifapentine C_{max} and AUC ranging from 36% to 44% under fasted conditions.*

Table 6. Treatment ratio estimates (rifapentine with isoniazid versus rifapentine alone) with 90% CIs for rifapentine PK parameters

Comparison	Parameter	Estimate	90% CI
Rifapentine + isoniazid fasted versus rifapentine fasted	C_{max}	0.94	(0.76 to 1.17)
	AUC_{last}	0.91	(0.73 to 1.14)
	AUC	0.91	(0.72 to 1.15)
	$t_{1/2z}$	0.95	(0.87 to 1.04)

Rifapentine + isoniazid fasted versus rifapentine fasted = Rifapentine 900 mg + isoniazid 900 mg fasted versus rifapentine 900 mg fasted

For 25-desacetyl-rifapentine Cmax, AUClast and AUC, the ratio estimates (rifapentine with isoniazid versus rifapentine alone) were within the protocol specified range [0.8 - 1.25] but the lower limit of the confidence interval was below 0.8 (**Table 7**).

Table 7. Treatment ratio estimates (rifapentine with isoniazid versus rifapentine alone) with 90% CIs for 25-desacetyl-rifapentine PK parameters

Comparison	Parameter	Estimate	90% CI
Rifapentine + isoniazid fasted versus rifapentine fasted	C_{max}	0.91	(0.72 to 1.15)
	AUC_{last}	0.88	(0.69 to 1.13)
	AUC	0.89	(0.68 to 1.15)
	$t_{1/2z}$	1.00	(0.85 to 1.18)

Rifapentine + isoniazid fasted versus rifapentine fasted = Rifapentine 900 mg + isoniazid 900 mg fasted versus rifapentine 900 mg fasted

Reviewer Comment: *The changes in 25-desacetyl-rifapentine C_{max} and AUC (9 and 11%, respectively) when rifapentine is co-administered with isoniazid were less than the inter-individual variability of 25-desacetyl-rifapentine C_{max} and AUC ranging from 59% to 66% under fasted conditions.*

For isoniazid, all 90% CIs of C_{max} and AUCs ratios (isoniazid with rifapentine versus isoniazid alone) were inside the interval [0.8; 1.25] thus demonstrating the lack of pharmacokinetic interaction of rifapentine on isoniazid (**Table 8**).

Table 8. Treatment ratio estimates (rifapentine with isoniazid versus rifapentine alone) with 90% CIs for isoniazid PK parameters

Comparison	Parameter	Estimate	90% CI
Rifapentine + isoniazid fasted versus isoniazid fasted	C_{max}	0.94	(0.81 to 1.10)
	AUC_{last}	0.97	(0.92 to 1.03)
	AUC	0.97	(0.92 to 1.03)
	$t_{1/2z}$	1.02	(0.98 to 1.06)

Rifapentine + isoniazid fasted versus isoniazid fasted = Rifapentine 900 mg + isoniazid 900 mg fasted versus isoniazid 900 mg fasted

Food Effect

An increase of 47% in rifapentine C_{max} and of 51% in AUC was observed when rifapentine and isoniazid are administered with a low fat, high carbohydrate breakfast (**Table 9**).

Table 9. Food ratio estimates (rifapentine co-administered with isoniazid in fasted and fed conditions) with 90% CIs for rifapentine PK parameters.

Comparison	Parameter	Estimate	90% CI
Rifapentine 900 mg + isoniazid 900 mg (fed versus fasted)	C_{max}	1.47	(1.24 to 1.74)
	AUC_{last}	1.50	(1.26 to 1.80)
	AUC	1.51	(1.25 to 1.82)
	$t_{1/2z}$	1.02	(0.91 to 1.14)

Rifapentine 900 mg +isoniazid 900 mg (fed versus fasted) = Rifapentine 900 mg +isoniazid 900 mg fed versus rifapentine 900 mg +isoniazid 900 mg fasted

An increase of 44% and 51% in 25-desacetyl-rifapentine C_{max} and AUC was observed when rifapentine and isoniazid are administered with a low fat, high carbohydrate breakfast. There was no significant food effect on 25-desacetyl-rifapentine $t_{1/2z}$ (**Table 10**).

Table 10. Food ratio estimates (rifapentine with isoniazid in fed versus in fasted condition) with 90% CIs for 25-desacetyl-rifapentine PK parameters

Comparison	Parameter	Estimate	90% CI
Rifapentine 900 mg+isoniazid 900 mg (fed versus fasted)	C_{max}	1.44	(1.14 to 1.82)
	AUC_{last}	1.49	(1.17 to 1.91)
	AUC	1.51	(1.17 to 1.95)
	$t_{1/2z}$	1.02	(0.89 to 1.16)

Rifapentine 900 mg +isoniazid 900 mg (fed versus fasted) = Rifapentine 900 mg +isoniazid 900 mg fed versus rifapentine 900 mg +isoniazid 900 mg fasted

In contrast, a decrease of 46% and 23% in isoniazid C_{max} and in AUC was observed when isoniazid and rifapentine are administered with a low fat, high carbohydrate breakfast (**Table 11**).

Table 11. Food ratio estimates (rifapentine co-administered with isoniazid in fasted and fed conditions) with 90% CI for isoniazid PK parameters

Comparison	Parameter	Estimate	90% CI
Rifapentine 900 mg+isoniazid 900 mg (fed versus fasted)	C_{max}	0.54	(0.45 to 0.65)
	AUC_{last}	0.77	(0.68 to 0.87)
	AUC	0.77	(0.68 to 0.87)
	$t_{1/2z}$	1.27	(1.13 to 1.43)

Rifapentine 900 mg +isoniazid 900 mg (fed versus fasted) = Rifapentine 900 mg +isoniazid 900 mg fed versus rifapentine 900 mg +isoniazid 900 mg fasted

The food effect on C_{max}, AUC_{last} and AUC of rifapentine and 25-desacetyl rifapentine were shown to be different in male and female subjects ($p<0.01$). Based on estimates ratio values in male and female subjects, the food effect was not significant (within ±10%) in female subjects; whereas, in male, the concomitant administration of rifapentine with food increases its bioavailability by 70 to 80%. For isoniazid, no gender effect was observed.

Safety:
There were no serious adverse events (SAEs) and all treatment emergent adverse events (TEAEs) were mild in intensity. For all treatment periods, potential clinically significant abnormalities (PCSAs) for laboratory values were infrequent. Regarding the vital signs, PCSAs for elevated systolic blood pressure (SBP), diastolic blood pressure (DBP) or heart rate (HR) were reported in 2 subjects including one subject who discontinued due to mild TEAE of elevated blood pressure during isoniazid alone treatment. PCSAs for ECGs were reported in 3 subjects including two subjects with a borderline increase in QTc interval during the rifapentine + isoniazid fed treatment and one subject with an increase in heart rate (reported as TEAE of nodal arrhythmia), 6 days following rifapentine fasted administration.

SPONSOR'S CONCLUSIONS

Safety

Overall, single administration of rifapentine or isoniazid was generally tolerable in healthy male or female subjects when administered alone and in combination in fed or fasted conditions.

Pharmacokinetics

Co-administration of rifapentine and isoniazid (900 mg single doses), in fasted condition, did not result in significant change of exposure of rifapentine or isoniazid compared as when administered alone in fasted condition. The administration of rifapentine and isoniazid (900 mg single doses), concomitant with a low fat, high carbohydrate breakfast, led to an increase of rifapentine bioavailability 47% in C_{max} and 51% in AUC. In contrast, the concomitant administration of food, led to a decrease of isoniazid bioavailability with a reduction of 46% in C_{max} and of 23% in AUC.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results.

STUDY NO.: IHH0013

Evaluation of the potential induction effect of rifapentine and 25-desacetyl rifapentine on CYP1A, CYP2B6 and CYP3A enzyme activities and gene expression using human hepatocytes in primary culture

OBJECTIVE(S): To evaluate the potential induction effect of rifapentine on CYP1A, CYP2B6 and CYP3A enzyme activities and CYP1A2, CYP2B6 and CYP3A4 gene expression, in primary cultures of human hepatocytes.

METHODS

This study evaluated the potential induction effect of rifapentine and 25-Desacetyl rifapentine on CYP1A, CYP2B6 and CYP3A gene expression and enzyme activities, in primary cultures of human hepatocytes. Each experiment was conducted with 3 human hepatocyte preparations from 3 donors. Human primary hepatocyte cultures were treated daily for 2 consecutive days for gene expression and for three consecutive days (approximately 72 hours) for enzyme activities with rifapentine and 25-Desacetyl rifapentine at concentrations ranging between 0.01 and 30 µM. Omeprazole, phenobarbital and rifampicin were used as positive control inducers for CYP1A, CYP2B6 and CYP3A4, respectively. The final solvent (DMSO) concentration in the incubation medium was 0.1% in all cases.

Incubation with probe substrates

Measurement of marker metabolites

CYP1A-, CYP2B6-, and CYP3A-catalyzed activities were evaluated by measuring the rate of appearance of their respective specific metabolites, 4-acetamidophenol, hydroxyl-bupropion and the sum of 1'-hydroxymidazolam and 1'OH-midazolam glucuronide. Amounts of metabolites formed in the incubation mixture were assessed according to LC-MS/MS methods.

Stability of rifapentine and 25-desacetyl rifapentine

The concentration of parent drugs in the medium i.e., rifapentine and 25-desacetyl rifapentine, was measured at several time points (0, 1, 6 and 24 hours in duplicate) the last day of the incubation for determining the actual drug exposure surrounding the cells.

Analytical Methods: Amounts of metabolites formed in the incubation mixture were assessed by LC-MS/MS. The limit of quantification (LOQ) was 0.039 µM for 4-acetamidophenol, OH-bupropion, 1'OHmidazolam and 1'OH-midazolam glucuronide.

Data Analysis:

Measurement of gene expression

Both the gene of interest and the housekeeping gene (β2M) amounts (MFI) were determined in two different tubes of the same sample. Then an average of the two values is determined (Mean). The background was subtracted. For data obtained from the same sample, the measured amount of the gene of interest was normalized to the amount obtained for the housekeeping gene in that sample. All results were expressed as the expression level of the investigated gene in treated hepatocytes, relative to control conditions.

Measurement of enzyme activities

Activity of CYP1A, CYP2B6 or CYP3A in the hepatocyte samples were determined by quantifying the production of the specific probe metabolites. Rate of metabolite formation was expressed in nmol/h/106 cells using the following equation:

RESULTS

Effect of Rifapentine and 25-Desacetyl Rifapentine on CYP1A2, 2B6, and 3A4 mRNA Expression

As shown in **Table 1**, no significant effect of rifapentine or 25-desacetyl rifapentine was observed up to 30 µM on CYP1A2 gene expression for all human hepatocyte preparations. Rifapentine induced CYP2B6 gene expression in all donors with a maximum individual % of positive control (phenobarbital) at 61% and mean EC_{50} and E_{max} of 3.60 µM and 4.02-fold, respectively. 25-desacetyl-rifapentine induced CYP2B6 gene expression in all donors with a maximum individual % of positive control at 56% and mean EC_{50} and E_{max} of 11.7 µM and 3.57-fold, respectively. EC_{50} and E_{max} values for rifampicin were 1.3 µM and 5.66-fold, respectively.

Rifapentine induced CYP3A4 gene expression in all donors with a maximum individual % of positive control (rifampicin) at 107% and mean EC_{50} and E_{max} of 2.52 µM and 28.7-fold, respectively. 25-desacetyl rifapentine induced CYP3A4 gene expression in all donors with a maximum individual % of positive control at 88% and mean EC_{50} and E_{max} of 3.07 µM and 21.8-fold, respectively. EC_{50} and E_{max} values for rifampicin were 1.07 µM and 32.2 fold, respectively.

Table 1. Estimation of E_{max} and EC_{50} for rifapentine, 25-desacetyl rifapentine, Omeprazole, Phenobarbital and Rifampicin induction of CYP1A2, CYP2B6 and CYP3A4

Treatment		mRNA level: EC_{50} and E_{max}											
		CYP1A2 – mRNA expression				CYP2B6 – mRNA expression				CYP3A4 – mRNA expression			
		CD-Hu4237 (Cryo*)	BD-295 (Cryo*)	IVT-IBG (Cryo*)	Mean (SD)	CD-Hu4237 (Cryo*)	BD-295 (Cryo*)	IVT-IBG (Cryo*)	Mean (SD)	CD-Hu4237 (Cryo*)	BD-295 (Cryo*)	IVT-IBG (Cryo*)	Mean (SD)
Omeprazole	EC_{50} (µM)	10.6	31.3	47.6	29.8 (18.5)	19.1	29.4	25.3	24.6 (5.19)	6.00	28.0	23.8	19.3 (11.7)
	E_{max} (FI)	690	69.2	202	320 (327)	6.95	4.59	3.64	5.06 (1.70)	5.52	8.81	8.29	7.54 (1.77)
Phenobarbital	EC_{50} (µM)	NA	NA	NA	NA	610	162	474	415 (230)	290	248	283	274 (22.5)
	E_{max} (FI)	NA	NA	NA	NA	9.92	8.15	5.91	7.99 (2.00)	15.2	26.6	23.0	21.6 (5.84)
Rifampicin	EC_{50} (µM)	NA	NA	NA	NA	1.00	1.51	1.45	1.32 (0.28)	0.64	1.33	1.23	1.07 (0.37)
	E_{max} (FI)	NA	NA	NA	NA	6.27	6.12	4.60	5.66 (0.92)	21.2	52.6	22.7	32.2 (17.7)
rifapentine	EC_{50} (µM)	NA	NA	NA	NA	1.61	7.56	1.64	3.60 (3.43)	1.32	4.45	1.78	2.52 (1.69)
	E_{max} (FI)	NA	NA	NA	NA	4.48	4.44	3.14	4.02 (0.76)	19.2	52.0	14.8	28.7 (20.3)
25-desacetyl rifapentine	EC_{50} (µM)	NA	NA	NA	NA	10.7	14.2	10.3	11.7 (2.15)	1.49	4.37	3.34	3.07 (1.46)
	E_{max} (FI)	NA	NA	NA	NA	4.76	3.60	2.35	3.57 (1.21)	18.5	40.4	6.35	21.8 (17.3)

Additional Information:

NA: Not Applicable – *cryo: cryopreserved hepatocytes – FI: Fold Induction – SD: Standard Deviation

E_{max} and EC_{50} parameters were determined based on fold induction values, using a sigmoid curve fitting, obtained with BIOST@T-SPEED software

Fold induction = $E_{compound}$ / $E_{vehicle\ control}$

E_{max}: Maximal fold induction

EC_{50}: Concentration resulting in half-maximal induction

Effect of Rifapentine and 25-Desacetyl Rifapentine on CYP1A2, 2B6, and 3A4 Enzyme Activity

The percentage of positive control and the fold induction over vehicle control for CYP1A, CYP2B6 and CYP3A enzyme activities resulting from treatment with rifapentine and 25-desacetyl rifapentine are presented in **Table 2**.

No significant effect of rifapentine or 25-desacetyl rifapentine was observed up to 30 µM on CYP1A enzyme activity for all human hepatocyte preparations. Rifapentine and 25-desacetyl-Rifapentine induced CYP2B6 enzyme activity in all donors with maximum individual % of positive control at 74% and 31%, respectively. rifapentine and 25-desacetyl-Rifapentine induced

CYP3A enzyme activity in all donors with maximum individual % of positive control at 113% and 76%, respectively.

Table 2. CYP1A, CYP2B6 and CYP3A enzyme activities expressed as % positive control after a 72-hour treatment with rifapentine, 25-desacetyl rifapentine or the reference positive inducers

Treatment		Enzyme Activity: % positive control (Fold-induction)								
		CYP1A - phenacetin-O-deethylase			CYP2B6 - bupropion hydroxylase			CYP3A - midazolam hydroxylase		
		CD-Hu4237 (Cryo*)	BD-295 (Cryo*)	IVT-IBG (Cryo*)	CD-Hu4237 (Cryo*)	BD-295 (Cryo*)	IVT-IBG (Cryo*)	CD-Hu4237 (Cryo*)	BD-295 (Cryo*)	IVT-IBG (Cryo*)
Vehicule: DMSO	0.1%	0 (1.00)	0 (1.00)	0 (1.00)	0 (1.00)	0 (1.00)	0 (1.00)	0 (1.00)	0 (1.00)	0 (1.00)
Omeprazole	3 µM	22 (33.1)	22 (6.87)	6 (2.23)	NA	NA	NA	NA	NA	NA
	10 µM	64 (92.6)	59 (16.7)	28 (6.59)	NA	NA	NA	NA	NA	NA
	30 µM	**100 (144)**	**100 (27.7)**	**100 (20.9)**	NA	NA	NA	NA	NA	NA
	100 µM	21 (31.0)	49 (14.2)	49 (10.8)	NA	NA	NA	NA	NA	NA
Phenobarbital	100 µM	NA	NA	NA	26 (1.94)	48 (4.53)	17 (1.53)	NA	NA	NA
	300 µM	NA	NA	NA	61 (3.23)	66 (5.91)	44 (2.38)	NA	NA	NA
	1000 µM	NA	NA	NA	**100 (4.63)**	**100 (8.40)**	**100 (4.17)**	NA	NA	NA
	3000 µM	NA	NA	NA	167 (7.05)	157 (12.6)	113 (4.58)	NA	NA	NA
Rifampicin	1 µM	NA	NA	NA	NA	NA	NA	92 (9.03)	78 (1.89)	97 (3.08)
	3 µM	NA	NA	NA	NA	NA	NA	103 (9.98)	102 (2.16)	70 (2.49)
	10 µM	NA	NA	NA	NA	NA	NA	**100 (9.73)**	**100 (2.14)**	**100 (3.13)**
Treatment		Enzyme Activity: % positive control (Fold-induction)								
		CYP1A - phenacetin-O-deethylase			CYP2B6 - bupropion hydroxylase			CYP3A - midazolam hydroxylase		
		CD-Hu4237 (Cryo*)	BD-295 (Cryo*)	IVT-IBG (Cryo*)	CD-Hu4237 (Cryo*)	BD-295 (Cryo*)	IVT-IBG (Cryo*)	CD-Hu4237 (Cryo*)	BD-295 (Cryo*)	IVT-IBG (Cryo*)
Rifampicin	30 µM	NA	NA	NA	NA	NA	NA	96 (9.36)	84 (1.96)	78 (2.66)
rifapentine	1 µM (0.877 µg/mL)	1 (2.88)	0 (0.93)	0 (1.03)	37 (2.35)	28 (3.05)	31 (1.99)	90 (8.88)	84 (1.96)	84 (2.79)
	3 µM (2.63 µg/mL)	2 (3.65)	0 (1.09)	1 (1.20)	59 (3.16)	42 (4.08)	74 (3.34)	98 (9.55)	96 (2.09)	113 (3.40)
	10 µM (8.77 µg/mL)	2 (3.37)	0 (0.94)	0[#] (0.88)	62 (3.25)	44 (4.25)	62 (2.97)	94 (9.19)	106 (2.21)	93 (2.99)
	30 µM (26.3 µg/mL)	0 (0.80)	0 (1.13)	0[#] (0.70)	19 (1.70)	37 (3.75)	6 (1.18)	46 (4.98)	74 (1.84)	18 (1.39)
25-desacetyl rifapentine	1 µM (0.835 µg/mL)	0 (1.35)	1 (1.20)	0 (1.09)	3 (1.10)	11 (1.83)	6 (1.19)	18 (2.61)	26 (1.29)	11 (1.23)
	3 µM (2.51 µg/mL)	1 (2.38)	1 (1.39)	2 (1.32)	10 (1.37)	20 (2.45)	8 (1.24)	40 (4.53)	51 (1.58)	36 (1.76)
	10 µM (8.35 µg/mL)	1 (2.82)	1 (1.28)	2 (1.44)	20 (1.74)	17 (2.25)	31 (1.99)	57 (5.96)	76 (1.86)	52 (2.11)
	30 µM (25.1 µg/mL)	0 (1.33)	1 (1.32)	1 (1.14)	29 (2.06)	30 (3.19)	30 (1.96)	73 (7.35)	73 (1.84)	35 (1.76)

Additional Information:

In bold characters are highlighted the values for each reference inducer

All negative "% of positive control" values are reported as 0 ([#]).

NA: Not Applicable – *cryo: cryopreserved hepatocytes

$$(\%)\ \text{of positive control} = \frac{E_{compound} - E_{vehicle\ control}}{E_{positive\ control} - E_{vehicle\ control}} \times 100\% \qquad \text{Fold induction} = E_{compound} / E_{vehicle\ control}$$

$E_{compound}$: enzyme activity following compound-treatment

$E_{positive\ control}$: enzyme activity following inducer-treatment (omeprazole at 30 µM for CYP1A, phenobarbital at 1 mM for CYP2B6 and rifampicin at 10 µM for CYP3A)

$E_{vehicle\ control}$: enzyme activity following vehicle-treatment

Stability of Rifapentine and 25-Desacetyl Rifapentine

The concentration of parent drugs in the medium *i.e.*, rifapentine and 25-desacetyl rifapentine, was measured at several time points (0, 1, 6 and 24 hours in duplicate) on the third day of induction.

Over the 1-30 µM rifapentine concentration-range, rifapentine was demonstrated to be metabolized, with only 13 ± 9%, 21 ± 12%, 28 ± 16%, 30 ± 13% of unchanged rifapentine remaining at the 24th hour after a three day daily incubation of 1, 3, 10 and 30 µM rifapentine, respectively. Under these experimental conditions, increasing concentrations of 25-desacetyl rifapentine were formed.

Over the 1-30 μM 25-desacetyl rifapentine concentration-range, 25-desacetyl rifapentine was demonstrated to be not or very slowly metabolized, with 143 ± 13%, 93 ± 2%, 89 ± 1%, 87 ± 2% of unchanged 25-desacetyl rifapentine remaining at the 24th hour after a three-day daily incubation of 1, 3, 10 and 30 μM 25-desacetyl rifapentine, respectively.

SPONSOR'S CONCLUSIONS

- CYP1A: rifapentine and 25-desacetyl rifapentine at concentrations up to 30 μM induced neither CYP1A enzyme activity, nor CYP1A2 gene expression.
- CYP2B6: rifapentine and 25-desacetyl rifapentine induced CYP2B6 enzyme activity and gene expression in all tested donors with mean EC_{50} and E_{max} at 3.60 μM and 4.02-fold for rifapentine, and 11.7 μM and 3.57-fold for 25-desacetyl rifapentine.
- CYP3A: rifapentine and 25-desacetyl rifapentine induced CYP3A enzyme activity and CYP3A4 gene expression in all tested donors with mean EC_{50} and E_{max} at 2.52 μM and 28.7-fold for rifapentine, and 3.07 μM and 21.8-fold for 25-desacetyl rifapentine.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results.

4.2 Pharmacometric Review

1 SUMMARY OF FINDINGS

This population pharmacokinetic (PK) analysis characterizes the pharmacokinetics of rifapentine (RPT) and its main metabolite 25-desacetyl-rifapentine (25-des-RPT) based on the combined dataset from 4 clinical studies in children, healthy adolescents and adult patients with active or latent tuberculosis infection (LTBI) where rifapentine was administered either as a single dose or weekly doses: two Phase 1 clinical studies (children, adolescents), one Phase 1/2 clinical study (TBTC Study 25) and one Phase 3 clinical study (TBTC Study 26).

The population PK analysis comprised a total of 1634 rifapentine and 25-desacetyl-rifapentine serum concentrations from 227 subjects including children, adolescents, and adults, either healthy or with active/latent tuberculosis, who received a range of 300 -1200 mg oral doses of rifapentine as a single agent (children, adolescents), or in combination with isonazide (INH) in TBTC Study 25 and TBTC Study 26. Serum concentration data of RPT and 25-des-RPT were modeled simultaneously using a population PK analysis approach to estimate RPT and 25-des-RPT population PK parameters (mean and inter-patient variability) as well as the relationship between PK parameters and relevant patient covariates.

The structural model that best described the pharmacokinetics of rifapentine was a one-compartment model with a transit compartment chain for description of the absorption delay. Apparent oral clearance and volume of distribution parameters included body weight as a power-law covariate with exponents fixed to traditional allometric scaling values (i.e., 0.75 for clearance and 1 for volume). The following typical population estimates (% RSE) of rifapentine pharmacokinetics were obtained for a typical 70 kg patient: apparent oral clearance (CL/F) 2.32 L/h (11 %); apparent central volume of distribution (V_c/F) 51.7 L (10 %); absorption rate constant (k_a) 1.69 (34) h^{-1}, mean transit time (MTT) 0.62 h (27) and number of transit compartments (n) 1.8 (76). The inter-patient variability was 40% (13 %) for CL/F, 47%, (15 %) for V/F, and 90% (47 %) for MTT.

The structural model that best described the pharmacokinetics of 25-des-RPT was a one-compartment model. The typical population estimates (%RSE) of 25-des-RPT apparent clearance (CL_m/F_m) and apparent volume (V_m/F_m) for a 70 kg patient were 2.05 L/h (10 %) and 21.9 L (7 %), respectively. The inter-patient variability was 64% (18 %) for CL_m/F_m.

Body weight normalized apparent clearance (L/h/kg) was significantly higher in children than adults. This relation was described by a maturation function, where clearance for the youngest child (age, 2 y) was 0.052 L/h/kg, decreasing to the fully matured value of 0.026 L/h/kg by older age (half-life, 1.5 y (38% RSE), resulting with fully matured value by approximately age 10). Relative bioavailability of rifapentine in fasting condition for higher doses, 900 mg and 1200 mg compared to the lowest available dose in adults (600 mg) was found to be 0.96 (19% RSE) and 0.76 (16% RSE) respectively. Food increased relative bioavailability by 40% (8% RSE). Children who received crushed tablets had 26% (36% RSE) decreased relative bioavailability. There was no autoinduction with once-weekly dosing. Gender and race were evaluated as covariates during the population PK analysis but neither covariate was associated with a significant effect on rifapentine pharmacokinetics.

1.1 Key Review Questions

The purpose of this review is to address the following key questions:

1. Does the evaluated pediatric dosing result in comparable pediatric rifapentine exposures (AUC, C_{24}) to those observed in adults?

Results from this PK substudy demonstrated that rifapentine exposures were not comparable between children (ages 2 to 11 years) receiving weight-based dosing and adults receiving rifapentine 900 mg. The dosing algorithm used in TBTC Study 26 in children (aged 2 to 11 years) produced approximately 31% higher mean rifapentine AUC in Children compared to mean rifapentine AUC in adults receiving a standard 900-mg dose (720 versus 551 µg*h/mL; **Table 1.1-1**). Rifapentine AUC was 60% higher in children administered whole tablets (884 versus 551 µg*h/mL) and 19% higher in children administered crushed tablets (656 versus 551 µg*h/mL), as compared to exposures in adults (**Table 1.1-1**). The similar trend was observed with the AUC of 25-desacetyl-rifapentine in children compared to adults. Previous studies showed that rifapentine concentrations at 24 hours post-dose (C_{24}) correlated well with rifapentine AUC. The results derived from observed rifapentine C_{24} agree with those derived from AUC predicted by the population PK model (**Table 1.1-1**).

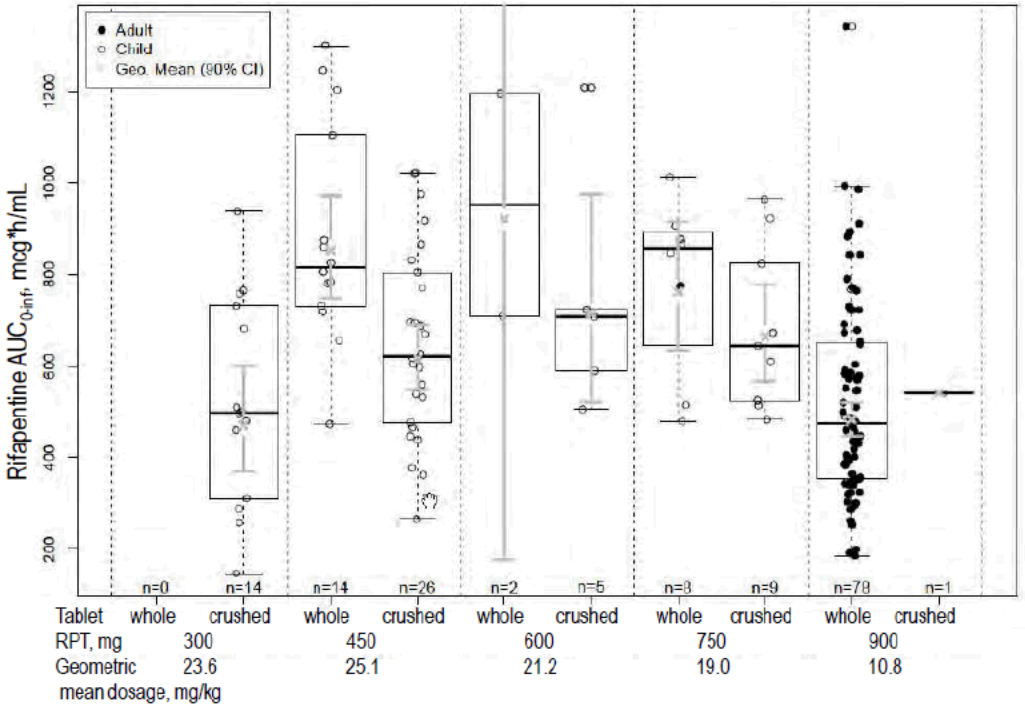
Table 1.1-1 Model Predicted AUC and Observed C_{24} of Rifapentine by Tablet Integrity

Rifapentine	Children			Adult N=77
	All children N=80	Whole Tablet N=25	Crushed Tablet N=55	
Model Predicted AUC (µg*h/mL)				
Geometric Mean	720	884	656	551
CV%	38	26	39	0.36
Geometric Mean Ratio (vs. Adults) *p*-value (vs. Adults)*	1.31 <0.0001	1.60 <0.0001	1.19 0.005 {0.0004†}	N.A.
Observed C_{24} (µg/mL)				
Geometric Mean	10.9	14.1	9.7	8.5
CV%	57	33	61	0.48
Geometric Mean Ratio (vs. Adults) *P*-value (vs. Adults)*	1.28 0.002	1.66 <0.0001	1.14 0.16 {0.001†}	N.A.

Note: AUC and C_{24} data are extracted from Sponsor's report of TBTC Study 26 PK, Table S11. Results from Reviewer's analysis on C_{24} agree with those from Sponsor's analysis.
**P-value based on t-test on log_e transformed data in comparison of all children vs. adults and by Fisher's LSD in each children group (whole or crushed tablet) vs. adults. † P-value by Fisher's LSD for comparison between children administered whole vs. crushed rifapentine tablets.*

The weight-based dosing algorithm used in TBTC Study 26 achieved 30-60% higher rifapentine exposure (both predicated AUC and observed C_{24}) in all children, except the 10-14 kg group, compared to adults (**Figure 1.1-1** and **Table 1.1-2**). The 10.0-14.0 kg weight band was comprised of 13 children (mostly aged 2-4 years), all of whom received crushed tablets and presented with slightly lower rifapentine exposure than adults (**Figure 1.1-1** and **Table 1.1-2**). Comparisons within pediatric weight bands between pediatrics administered crushed and whole rifapentine tablets demonstrated consistently 26% lower rifapentine exposures in the pediatric patients administered crushed rifapentine tablets (**Table 3.3.5-1**). One possible explanation is that children may not consume the entire quantity of the crushed tablet given with soft food or liquid. Population PK analysis also showed that food increased rifapentine exposure (both predicated AUC and observed C_{24}) in both children (by 25-30%; $p=0.23$) and adults (by 40%; $p<0.0001$) (**Table 1.1-3**). Therefore, children in the lowest weight band (10-14 kg) who take crushed tablets with food would be expected to achieve comparable exposure to adults.

Figure 1.1-1. Model Predicted Rifapentine AUC (Top Panel; Sponsor's Analysis) and Observed C_{24} (Bottom Panel; Reviewer's Analysis) by Rifapentine Dose (Weight Band) and Tablet Integrity (Crushed or Whole)



Note: Adapted from Sponsor's report of TBTC Study 26 PK, Figure S2.

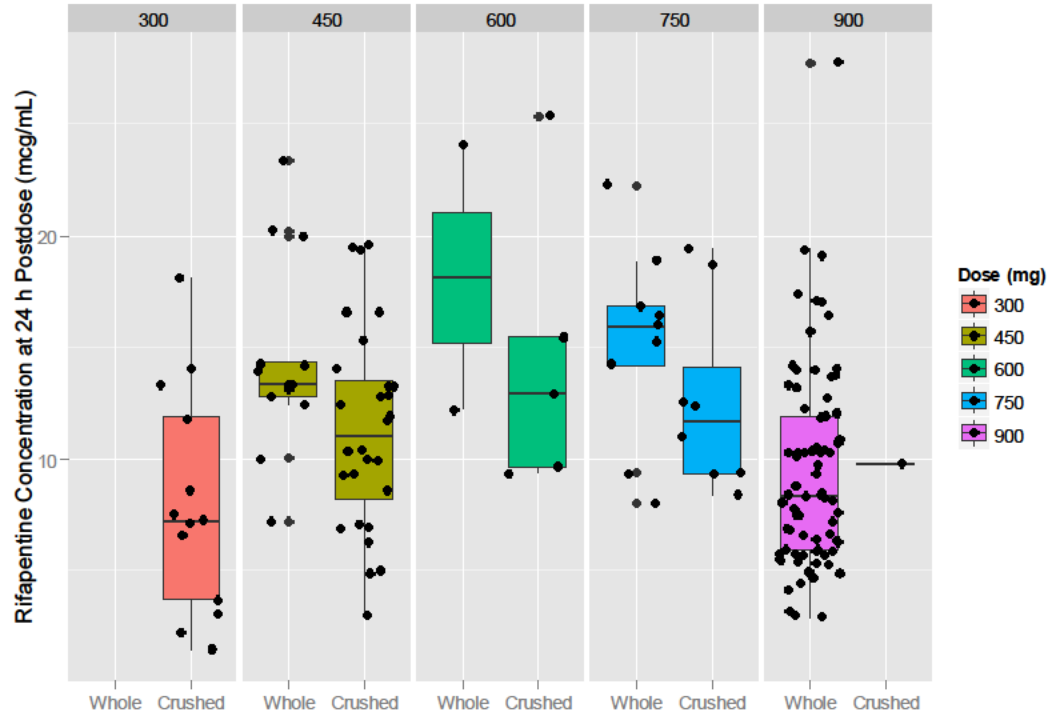


Table 1.1-2. Model Predicted Rifapentine AUC (Top Panel; Sponsor's Analysis) and Observed C_{24} (Bottom Panel; Reviewer's Analysis) by Rifapentine Dose (Weight Band) and Tablet Integrity (Crushed or Whole)

Weight Band (kg)	Age Group	RPT Dose (mg)	N	Tablet Integrity	Geometric Mean of RPT mg/kg[a]	RPT AUC (mcg*h/mL)						
						Geometric Mean RPT AUC (90% CI)	CV	Min	25th Percentile	Median	75th Percentile	Max
10.0-14.0	Child	300	13	Crushed	23.6	504 (399-637)	0.5	184.7	375.7	489.9	706.5	989.3
14.1-25.0	Child	450	26	Crushed	25.3	744 (684-810)	0.32	365.7	584.4	765.9	968.1	1301.4
		450	13	Whole								
25.1-32.0	Child	600	4	Crushed	21.3	762 (558-1041)	0.34	545	637.4	746.5	765.5	1297
		600	1	Whole								
32.1-50.0	Adult	750	1	Whole	18.7	813 (721-916)	0.28	539.5	615.6	883.9	1022.4	1184.2
	Child	750	8	Crushed								
		750	7	Whole								
>50	Adult	900	76	Whole	10.8	551 (517-588)	0.35	263.6	440.1	554.6	733.5	1300.7
	Child	900	1	Crushed								
		900	2	Whole								

Note: Adapted from Sponsor's report of TBTC Study 26 PK, Table S13. Table based on those participants who received the correct RPT dose for their weight band. Children that did not receive the correct RPT dose based on their weight band were removed. These include: 1 child in weight band 10.0-14.0 kg who received RPT 450 mg; 1 child in weight band 14.1-25.0 kg who received RPT 600 mg; 2 children in weight band 25.1-32.0 kg, where 1 received RPT 450 mg and the other received RPT 750 mg; and 1 child in weight band 32.1-50.0 kg who received RPT 600 mg.

[a]*Geometric Mean RPT mg/kg by RPT dose.*

Weight Band (kg)	Age Group	RPT Dose (mg)	N	Tablet Integrity	Geometric Mean of RPT mg/kg	RPT C_{24} (µg/mL)						
						Geometric Mean	CV	Min	25th Percentile	Median	75th Percentile	Max
10.0-14.0	Child	300	13	Crushed	23.6	6.4	0.88	1.4	3.7	7.2	11.9	18.1
14.1-25.0	Child	450	26	Crushed	25.3	11.3	0.47	3.0	9.3	12.8	14.2	23.4
			13	Whole								
25.1-32.0	Child	600	3	Crushed	21.3	14.0	0.43	9.6	11.6	12.6	16.1	25.3
			1	Whole								
32.1-50.0	Adult	750	1	Whole	18.7	13.0	0.31	8.0	8.3	13.4	16.6	19.4
	Child		8	Crushed								
			7	Whole								
>50	Adult	900	76	Whole	10.8	8.5	0.48	2.9	4.4	8.4	11.9	27.7
	Child		1	Crushed								
			2	Whole								

Table 1.1-3. Comparisons of Model Predicted Rifapentine AUC (Top Panel; Sponsor's Analysis) and Observed C_{24} (Bottom Panel; Reviewer's Analysis) in Both Children and Adults When Administered With and Without Food

Population	N	Geometric Mean RPT AUC (mcg*h/mL)	CV	Min	Max	90% CI	*P*-value*
Child with Food	70	740.3	0.34	283.0	1333.7	(693.1, 790.8)	0.23
Child with no Food	10	590.2	0.59	184.7	1095.5	(430.5, 809.0)	
Adult with Food	53	613.8	0.33	273.7	1300.7	(570.2, 660.8)	<0.0001
Adult with no Food	24	434.3	0.29	263.6	847.2	(393.3, 479.6)	

Note: Adapted from Sponsor's report of TBTC Study 26 PK, Table S18.
**P-value based on t-test using lognormal transformation.*

Population	N	Geometric Mean RPT C_{24} (µg/mL)	CV	Min	Max	90% CI	*P*-value
Child with Food	70	11.3	0.51	2.2	25.3	(11.0, 11.6)	0.33
Child without Food	10	8.7	0.93	1.4	19.5	(7.4, 9.9)	
Adult with Food	53	9.5	0.47	2.9	27.7	(9.1, 9.8)	0.0016
Adult without Food	24	6.7	0.42	3.0	17.0	(6.2, 7.3)	

2. Are the proposed pediatric dosing recommendations supported by observations from TBTC Study 26?

The proposed weight-based dosing regimen was used in pediatric patients (ages 2-11 years) enrolled in the TBTC Study 26. Despite the generally increased exposure observed in children 2 to 11 years of age in this PK substudy, an increase in the incidence or severity of adverse events (AEs) was not observed and no serious AEs were reported in any patients who participated in the PK substudy. The frequency of treatment-related AEs in Study 26 was similar for children enrolled in and not enrolled in the PK substudy (1.3% vs. 4.0%, respectively; p=0.421). In addition, although lower rifapentine exposure, compared to adults, was observed in younger children (mostly aged 2-4 years in the 10-14 weight band) who received crushed tablets, an decrease in efficacy was not observed as no pediatric patients on the 3RPT/INH arm in Study 26 developed TB disease over the 33-month follow-up period (primary clinical outcome). Therefore, the proposed pediatric dosing recommendations are supported by observations from TBTC Study 26.

1.2 Recommendations

The weight-based rifapentine dosing algorithm used in Study 26 appears appropriate for both safety and efficacy in pediatric patients (2-11 years) with LTBI. Rifapentine taken with food is recommended. Crushed rifapentine tablets can be administered to patients who cannot swallow whole tablets.

2 BACKGROUND

Priftin® (rifapentine) is an oral anti-mycobacterial agent derived from rifamycin. Rifapentine has been approved by FDA since June 1998 for the treatment of pulmonary tuberculosis (TB) caused

by *Mycobacterium tuberculosis* in patients ≥12 years. The approved therapeutic regimen consists of an initial 2-month phase followed by a 4-month continuation phase. The initial phase should be administered at a dose of 600 mg (4 x 150 mg tablets) twice weekly for two months by direct observation therapy (DOT), with an interval of no less than 3 consecutive days (72 hours) between doses, in combination with other anti-TB drugs as part of an appropriate regimen. The continuation phase may consist of Rifapentine (RPT) 600 mg once weekly for 4 months in combination with isoniazid (INH) or an appropriate anti-TB agent for susceptible organisms by DOT.

The Sponsor submitted a supplemental NDA on 5/30/2014. The proposed labeling changes contain the inclusion of a new indication for rifapentine in combination with INH in adults and children ≥ 2 years for the treatment of latent tuberculosis infection (LTBI). Rifapentine must always be used in combination with isoniazid (INH) for LTBI as a 12-week once-weekly regimen and administered by direct observation therapy (DOT) with dose determined by a bodyweight-based algorithm (the 3RPT/INH regimen).

RPT dose: Adjusted in 150 mg increments (from 300 to 900 mg) based on body weight:

Weight Range	Rifapentine Dose	Tablets
10.0-14.0 kg	300 mg	2 x 150 mg tablets
14.1-25.0 kg	450 mg	3 x 150 mg tablets
25.1-32.0 kg	600 mg	4 x 150 mg tablets
32.1-50.0 kg	750 mg	5 x 150 mg tablets
>50.0 kg	900 mg	6 x 150 mg tablets

INH dose:

- For patients 2 to 11 years old: 25 mg/kg (rounded up to nearest 50 or 100 mg; 900 mg maximum).
- For patients ≥ 12 years old: 15 mg/kg (rounded up to nearest 50 or 100 mg; 900 mg maximum).

The development program for the 3RPT/INH regimen in the treatment of LTBI is based mainly on Study TBTC-S26, in which the effectiveness and safety of 3RPT/INH was compared with a 9-month regimen of daily self-administered INH (9INH) in more than 8000 patients at high risk for developing TB disease. Also included in this sNDA submission are: 2 substudies in which enrollment was extended beyond the end of the TBTC-S26 main study in order to recruit additional children ≥2 years of age (TBTC-S26 pediatric substudy), to recruit additional HIV-infected patients not taking antiretroviral therapy (TBTC-S26 HIV substudy), and to conduct a pharmacokinetic substudy nested within Study TBTC-S26 (TBTC-S26 PK substudy) to evaluate the appropriateness of the weight-based dose algorithm in children (2 to 11 years old). Pharmacokinetic data from this pediatric PK substudy together with 3 previously completed PK studies in adults and children/adolescents form the basis of the population PK analysis.

3 RESULTS OF SPONSOR'S POPULATION PK ANALYSIS

Reviewer comment: Unless otherwise noted, the figures and tables displayed in section 3 reflect the sponsor's analyses from the current submission.

3.1 Objectives:

The overall objective of the analysis was to assess the population pharmacokinetics of rifapentine and 25-des-rifapentine after oral administration of rifapentine in children and adults with latent tuberculosis infection (LTBI). Specific aims of the analyses are the following:

Pharmacokinetics:

- To characterize rifapentine concentration-time profiles in children and adults after repeated treatment with rifapentine
- To estimate the magnitude of the inter-individual and intra-individual variability in rifapentine PK
- To identify covariates contributing/explaining inter- and intra-individual variability in rifapentine PK

Secondary:

- To characterize the pharmacokinetics of main metabolite (25-des-RPT)

3.2 Studies and Data Included in the PopPK Analysis

This population PK analysis evaluated data obtained from 4 clinical studies of rifapentine (TBTC Study 25, TBTC Study 26, children and adolescent study). A summary of the studies is provided in **Table 3.2-1.** PK profiles from a total of 227 subjects were used in this analysis. Additional details on each of the studies are provided below.

Table 3.2-1. Summary of Studies Included in the Population PK Analysis

Study	Phase	n [a]	Population	Treatment	DrugX Dose
TBTC 25	I/II	35	Adult Patients with TB	RPT+INH	600mg, 900mg, 1200mg weekly
TBTC 26	III	157	Children and Adults with LTBI	RPT + INH	300- 900mg weekly
children	I	23	Children w/o TB	RPT	150mg, 300mg single dose
adolescent	I	12	Healthy Adolescents	RPT	450mg, 600mg single dose

[a] *Number of subjects receiving RPT included in the population PK analysis*

TBTC Study 25

TBTC Study 25 was a prospective, double-blind, randomized Phase 2 trial to evaluate the tolerability of once-weekly, continuation phase, directly observed therapy with rifapentine at three doses (600, 900, and 1,200 mg) and isoniazid in 150 HIV-seronegative patients with drug-susceptible tuberculosis. The pharmacokinetic substudy included 35 adult patients with tuberculosis (continuation phase therapy) who received commercial formulation of rifapentine (600, 900, or 1200 mg once weekly) usually without food. Pharmacokinetic data were collected after $\geqslant$3 weeks of once-weekly treatment. Plasma samples for rifapentine and metabolite concentrations were collected (11 samples: pre-dose, 2, 4, 6, 8, 10, 12, 18, 24, 48, and 72 h post-dose).

TBTC Study 26 (PREVENT-TB Study)

TBTC Study 26 was a Phase 3, randomized treatment trial of 8,053 patients with LTBI, comparing a 12-dose, once-weekly rifapentine and isoniazid regimen to nine months of daily isoniazid. 161 patients were recruited into PK substudy from the Phase 3, PREVENT TB trial, of whom 157 had evaluable PK samples (80 children and 77 adults). Children enrolled in this substudy were age 2 to 11 years and all children and adults in the PK substudy were treated with 3RPT/INH. Rifapentine was administered as 150 mg tablets. Rifapentine doses in children ranged from 300 to 900 mg based on weight and dosage (**Table 3.2-2**) and the rifapentine dose in adults was 900 mg (all patients weighed more than 45 kg). Children who could not swallow tablets were administered a suspension of crushed rifapentine and isoniazid tablets in either a soft food or liquid. For children, the once-weekly dosage of isoniazid was 25 mg/kg, (900 mg maximum), and adults were administered isoniazid 15 mg/kg (900 mg maximum). After at least three once-weekly doses of rifapentine and isoniazid, a single plasma sample (C_{24}) was collected 24-hours (23 to 25 hours) after administration of study drugs for PK analysis of rifapentine and 25-des-RPT.

Table 3.2-2. Rifapentine dosing algorithm used for children in the PREVENT-TB study

Weight (kg)	Rifapentine dose (mg)	Rifapentine dosage (mg/kg)	Number of children in each group	Age of study patients (mean ± SD in years)
10-14	300	21-30	34	2.6 ±.8
>14-25	450	18-32	40	4.5 ± 1.6
>25-32	600	19-24	7	7.4 ± 2.2
>32-50	750	15-23	16	9.7 ± 2.4
>50	900	≤18	3	10.0 ± 1.0

Children study

The pharmacokinetic study in children included 23 children (age, 2 to 12 years) without tuberculosis. The children received rifapentine tablets (150 or 300 mg) without food. If a child had difficulty swallowing tablets, the tablets were crushed before administration (in 9 out of 23 children). Plasma samples for rifapentine and metabolite concentrations were collected (11 samples: pre-dose and 0.5, 1, 2, 3, 4, 6, 10, 12, 24, and 32 h post-dose).

Adolescent study

The pharmacokinetic study in adolescents included 12 healthy subjects (age, 12 to 15 years) who received rifapentine (1 dose; 450 mg for adolescents weighing < 45 kg or 600 mg for adolescents weighing >45 kg) without food. Plasma samples for rifapentine and metabolite concentrations were collected (11 samples: pre-dose and 2, 3, 4, 5, 6, 8, 12, 24, 48, and 72 h post-dose).

All available concentration-time points for rifapentine and 25-des-RPT were included in the analysis and no additional data exclusions were made. In total, there were 227 subjects and 1634 concentration-time measurements evaluated, including 767 plasma samples from 116 children (58 young females) and 867 samples from 114 adults. In children (age: median, 6 years; range, 2 to 15 years), median weight was 28 kg (range, 11 to 76 kg). A crushed tablet formulation was

received by 64 children, and the tablet was received with food in 70 children (all from the Study 26 PK substudy).

Table 3.2-3. Demographic and Clinical Features of Children and Adults in the Combined Data.

Feature	children	Adults
Number subjects	116	114
Age, median (range), y	6 (2 to 15)	41 (18 to 68)
Race		
Black, n (%)	13 (11)	30 (26)
White, n (%)	98 (85)	78 (69)
Asian, n (%)	5 (4)	6 (5)
Ethnicity, Hispanic	70 (60)	65 (57)
Gender, male, n (%)	58 (58)	64 (50)
HIV infection, n (%) [c]	0/5	1/54 (2)
Drug administration		
Whole tablets, n (%)	52 (64) [d]	114 (100)
With food, n (%)	70 (46)	55 (48)

Reviewer's comments: *The demographics of the patients in the population PK dataset were similar to the demographics of the overall population in the pivotal efficacy/safety study TBTC-S26, with the possible exception of race. Specifically, the overall population had a higher representation for Asians (12.4 % overall) and a lower representation of Whites (57.9 % overall). The study population was well balanced between children vs. adults, males vs. females, whole tablets vs. crushed tablets groups, and with food vs. without food groups, except for racial groups, which assisted in assessing the impact of these covariates (except for race) in the subsequent analysis. There were insufficient patients with race identified as Asian for identification of a covariate impact from the dataset used for the population PK analysis.*

3.3 Methods and Results

3.3.1 Structural Model Development

The schematic view of the model building strategy is shown in the **Figure 3.3.1-1** below.

Figure 3.3.1-1. Schematic view of the model building strategy

Children model development – Model I

A basic model structure was established with rich pharmacokinetic profiles from studies in children and adolescents. Different absorption and disposition model structures were evaluated. Body weight was included as a covariate on apparent oral clearance (CL/F) and apparent volume of distribution (V/F) using a power-law structure and exponents fixed to values traditionally associated with allometric scaling (CL/F with exponent 0.75 and V/F with exponent 1). A maturation function was included to describe the trend between individual clearance parameters and both weight and age. Partial covariate model with covariates of weight, age and tablet integrity was established at this step. Using this base model, pharmacokinetic profiles with sparse data from children in the PREVENT TB trial were predicted using visual predictive check. However, the initial base model predictions underestimated the observed data. Of note, rifapentine in the study 26 was administered with food; while in the previous studies, the drug was given on empty stomach. Given that the initial base model did not account for the effect of food on bioavailability, the food effect on bioavailability was incorporated in the model. At this stage, this model already included the following covariates: weight, age, tablet integrity (crushed versus whole), and food.

After the primary model was established, metabolite data were added. Initially, the rifapentine part of the model was held constant and different structures for the metabolite model were evaluated including 1- and 2-compartment disposition models. Similar to the rifapentine model, body weight was included as a covariate on CL/F and V/F for the metabolite model, and

exponents were fixed to values traditionally associated with allometric scaling (0.75 for CL/F and 1for V/F). In the final step, both rifapentine and metabolite data were fitted simultaneously.

Adult model development – Model II
The modeling strategy for adults was similar to that described for children. The basic model structure was developed using the pharmacokinetic data from TBTC Study 25. A function was added relating decreased bioavailability with rifapentine dose. Rifapentine (600 mg) in fast condition was used as a reference dose, and relative bioavailability was defined as 1 for this dose. Pharmacokinetic parameters were allometrically scaled to body weight as described above. This model was used to predict PK profiles using sparse data from PREVENT TB substudy; similar to the model for children, the food effect on bioavailability was incorporated into the model. Subsequently, all available adult rifapentine data were included, pharmacokinetic parameters were re-estimated, and the metabolite model was developed similar to that in children.

Joint children and adult model development – Model III
After the 2 models were developed for children and adults, these models were merged. Differences in pharmacokinetic behavior between children and adults were identified. Significant differences in pharmacokinetic parameters between children and adults were evaluated by fitting the 2-parameter model for the 2 populations and fitting 1 parameter for both populations. When merging parameters worsened the model fit, the parameters were kept separate.

Goodness-of-fit of the structural model was assessed by diagnostic plots:

- Observations versus population and individual predictions
- Population, individual and conditional weighted residuals versus time
- Above plots stratified by dose and study

3.3.2 Covariate Model Development
The covariates tested in the children model were: tablet crushed [yes/no], sex [58 F/ 58 M], age [median 6 years (min 2 – max 15)], weight [median 28 kg (min 11 – max 76)] and race (70 Hispanic, 13 Black, 28 Caucasian, 3 Asian). The covariates tested in the adult model were: sex [50 F/ 64 M], age [median 42 years (min 18 – max 68)], weight [median 76 kg (min 46 – max 169)] and race (65 Hispanic, 30 Black, 13 Caucasian, 6 Asian).

The goodness of fit and appropriateness of the covariate model were assessed by means of diagnostic plots as well as individual random effects (ETAs) estimates versus covariates, comparison with base model without covariates.

3.3.3 Final Population Model
Rifapentine pharmacokinetics was best described by a 1-compartment model linked to the transit compartment absorption model (**Figure 3.3.3-1**).

Figure 3.3.3-1. Schematic representation of the Final Model.

The final model was represented by equations 1 to 3 (**Table 3.3.3-1**), and the estimation of model pharmacokinetic parameters and the relation between covariates and parameters were represented by equations 4 to 8 (**Table 3.3.3-1**).

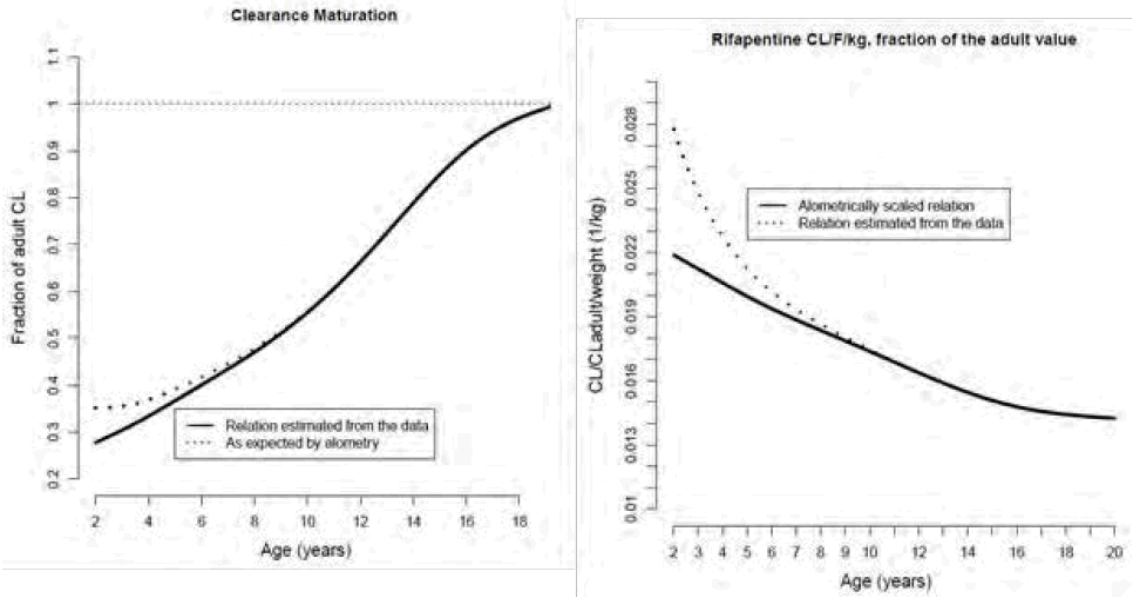
Table 3.3.3-1 Pharmacokinetic Model for Rifapentine and Metabolite 25-desacetyl-rifapentine in Children and Adults with Latent Tuberculosis Infection.

Equation no.	Description	Equation
1	RPT absorption kinetics	(b) (4)
2	RPT disposition kinetics	
3	25-des-RPT disposition kinetics	
4	RPT CL and its relationship with age and weight	
5	25-des-RPT clearance	
6	RPT central volume	
7	25-des-RPTcentral volume	
8	Bioavailability expression and its relationship to dose, crushing and food	

(b) (4)

Body weight normalized apparent oral clearance (L/hr/kg) was significantly higher in children than adults: clearance for the youngest child (age, 2 y; body weight, 12 kg) was 0.052 L/h/kg, decreasing to the fully matured value of 0.026 L/h/kg (adult clearance). The clearance in very young children was higher than that anticipated due solely to differences in body weight. To account for this additional observed difference in exposure between adults and pediatric, a maturation function was included in the model which improved the model fit significantly ($p<0.05$). Clearance maturation expected from growth (weight gain) and estimated in the model showed an increase in clearance in children that was dependent on age (**Figure 3.3.3-2**). As shown in below, the main impact of including this term was to alter model predicted pediatric clearance values in subjects with body weight <6 years of age.

Figure 3.3.3-2. Comparison of allometric scaling versus inclusion of a clearance maturation function for rifapentine.



Left: fraction of total adult clearance. Right: fraction of adult clearance normalized per kilogram body weight. CL, clearance; CL/F, clearance corrected for bioavailability

The estimated increase in clearance per kilogram body weight caused by increased metabolic activity was 22% for the youngest child (age, 2 years). An age-dependent relationship was not observed for metabolite clearance; the lower rifapentine/metabolite exposure ratios observed in very young children than adults could be due to higher metabolic activity in very young children.

Reviewer Comment: The additional increase in clearance in younger children was probably caused by increased metabolism (mediated by esterases), or increased renal function (although renal excretion only accounts for ~20% of rifapentine elimination), or an artifact of loss of the drug from tablet crushing.

The final parameter estimates for the Models I-III are given in **Table 3.3.3-2, Table 3.3.3-3,** and **Table 3.3.3-4**. Children who could not swallow the whole tablet, and received the formulation crushed, had a decrease in relative bioavailability (26%). Introduction of this relationship into the children model resulted in a significant decrease in the objective function value by 8.9 ($p<0.003$). There was no auto-induction with once-weekly dosing. In addition, administration with food had an effect of increasing bioavailability by 40%. Finally, decreasing bioavailability was observed with increasing dose based on the adult data. Estimated relative bioavailability in adults was 0.96 for the 900 mg dose and 0.76 for the 1200 mg dose, relative to the 600 mg dose. Between-subject variability in clearance was 40%.

Table 3.3.3-2. Population Mean and Relative Standard Errors for Population PK Parameter Estimates from the Final Children Model. Standard Errors were Obtained by Bootstrapping (n=100).

Parameter	Value (RSE, %)	Between subject variability, CV% (RSE, %)	Shrinkage (%)
CL/F for 35 kg person (L/h)	1.83 (34)	41 (21)	9
V/F for 35 kg person (L)	33.4 (6)	39 (21)	26
ka (h^{-1})	4.5 (32)	-	
Mean transit time (h)	1.95 (22)	72 (49)	52
Number of transit compartments	2.8 (47)	58 (149***)	68
Maximal age dependent increase in CL (fraction) , **	0.44 (37)	-	
Half-life (y) for age related change in CL/kg to disappear	2.6 (175***)	-	
Decrease in F with crushed tablet (fraction)	0.21 (33)	-	
CLm/Fm for 35kg person (L/h)	1.19 (7)	77 (26)	9
Vm/Fm for 35kg person (L)	10.5 (6)	-	
Correlation CL-CLm	0.9 (26)	-	
Food effect on bioavailability (fraction)	1.5 (FIXED)	-	
Proportional residual error, rifapentine, children (CV%)	14 (11)	-	
Additive residual error, rifapentine, children (ng/mL)	0.29 (42)	-	
Proportional residual error, metabolite, children (CV%)	14 (23)	-	
Additive residual error, metabolite, children (ng/mL)	0.45 (21)	-	

** Abbreviations: CL, clearance; CLM, clearance of 25-des-RPT; CV%, coefficient of variance; F, bioavailability; ka, absorption rate constant;; RSE, relative standard error; V, rifapentine volume of distribution.;*
*** Effect size parameter from the equation;*
**** Large relative standard errors are due unsymmetrical (one side tailed) uncertainty distribution)*

Reviewer comment: The shrinkage estimates for mean transit time and number of transit compartment are relatively large (> 50%). This may indicate model overparameterization and that transit absorption compartments could not be characterized in all patients based on the available PK data. As these parameters will primarily govern absorption dynamics, the identified model may not be appropriate for simulating pediatric C_{max} exposures for the proposed dosing regimen.

Table 3.3.3-3. Population Mean and Relative Standard Errors for Population PK Parameter Estimates from the Final Adults Model. Standard Errors were obtained by Bootstrapping (n=100)

Parameter	Value (RSE, %)	Between subject variability, CV% (RSE, %)	Shrinkage (%)
CL/F for 70 kg person (L/h)	1.97 (26)	37 (20)	7
V/F for 70 kg person (L)	47 (28)	47 (20)	13
Correlation CL-V	0.89 (20)	-	
ka (h^{-1})	0.82 (40)	82 (78)	
Mean transit time (h)	0.26 (84)	140 (169)	60
Number of transit compartments	3.1 (NA)***	-	
CLm/Fm for 70kg person (L/h)	2.2 (27)	54 (29)	8
Vm/Fm for 70kg person (L)	18.1 (23)	-	
Correlation CL-CLm	0.89 (27)	-	
Correlation V-CLm	0.73(31)		
Bioavailability of 900 mg dose	0.92 (31)	-	
Bioavailability of 1200 mg dose	0.77 (32)	-	
Food effect on bioavailability (fraction)	0.5 FIXED (NA)	-	
Proportional residual error, rifapentine, adults (CV%)	25 (10)	-	
Proportional residual error, metabolite, adults (CV%)	28(9)	-	

** Abbreviations: CL, clearance; CLM, clearance of 25-des-RPT; CV%, coefficient of variance; F, bioavailability; ka, absorption rate constant;; RSE, relative standard error; V, rifapentine volume of distribution.;*
*** Effsize parameter from the equation;*
**** Estimated standard error is very large due to asymmetric distribution of uncertainty, 90% CI for this parameter estimated by the same nonparametric bootstrap are 0,5-94.*

Reviewer comment: *The shrinkage estimates for mean transit time and number of transit compartment are relatively large (> 50%), similar to what was observed for the pediatric popPK model. As these parameters will primarily govern absorption dynamics, the identified model may not be appropriate for simulating adult C_{max} exposures.*

Table 3.3.3-4. Population Mean and 95% Confidence Interval for Population PK Parameter Estimates from the Final Joint Model

Parameter	Value (RSE, %)	Between subject variability, CV% (RSE, %)	Shrinkage (%)
CL/F for 70 kg person (L/h)	2.32 (11)	40 (13)	9
V/F for 70 kg person (L)	51.7 (10)	47 (15)	8
Correlation CL-V	0.758 (18)	-	
ka (h^{-1})	1.69 (34)	-	
Mean transit time (h)	0.62 (27)	90 (47)	16
Number of transit compartments	1.8 (76)	-	
Maximal age dependent increase in CL (fraction) , **	0.22 (23)	-	
Half-life (y) for age related change in CL/kg to disappear	1.49 (38)	-	
Decrease in F with crushed tablet (fraction)	0.26 (36)	-	
CLm/Fm for 70kg person (L/h)	2.05 (10)	64 (18)	67
Vm/Fm for 70kg person (L)	21.87 (7)	-	
Correlation CL-CLm	0.88 (17)	-	
Bioavailability of 900 mg dose	0.96 (19)	-	
Bioavailability of 1200 mg dose	0.76 (16)	-	
Food effect on bioavailability (fraction)	0.403 (8)	-	
Proportional residual error, rifapentine, children (CV%)	15 (10)	-	
Additive residual error, rifapentine, children (ng/mL)	0.62 (27)	-	
Proportional residual error, metabolite, children (CV%)	14 (18)	-	
Additive residual error, metabolite, children (ng/mL)	0.47 (14)	-	
Proportional residual error, rifapentine, adults (CV%)	29 (7)	-	
Proportional residual error, metabolite, adults (CV%)	31 (8)	-	

** Abbreviations: CL, clearance; CLM, clearance of 25-des-RPT; CV%, coefficient of variance; F, bioavailability; ka, absorption rate constant; RSE, relative standard error; V, rifapentine volume of distribution.;*
*** Effsize parameter from the equation 4*

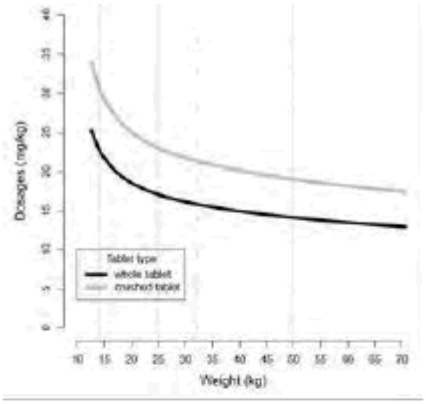
The required doses to reach target adult exposure (AUC) after a 900 mg dose of rifapentine with food were estimated for children of different age and body weight (**Table 3.3.3-5**). The dosing chart (dose and dosage mg/kg body weight) showed that in general higher doses of crushed tablets would be necessary compared to whole tablet dosing to achieve the target exposures (**Figure 3.3.3-3**).

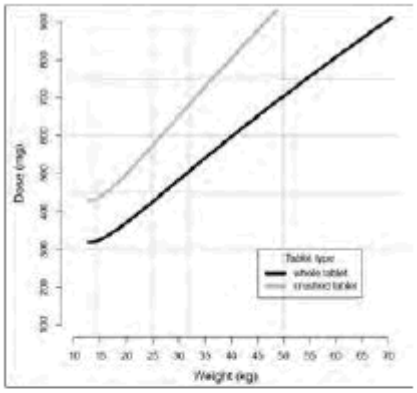
Table 3.3.3-5. Comparison of Rifapentine Dosing Algorithm Used for Children in the PREVENT-TB Study with Modeled Dosing *

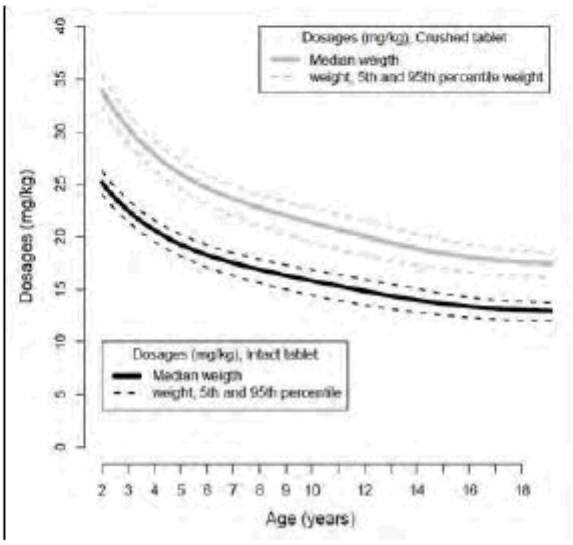
Body weight (kg)	Used (PREVENT TB trial)	Modeled (Intact tablet)	Modeled (Crushed tablet)
----------Rifapentine dose (mg) ----------			
10 to 14	300	266 to 320	359 to 431
> 14 to 25	450	320 to 425	431 to 573
> 25 to 32	600	425 to 506	573 to 682
> 32 to 50	750	506 to 703	682 to 948
> 50	900	> 703	> 948
----------Rifapentine dosage (mg/kg)----------			
10 to 14	21 to 30	23 to 27	31 to 36
> 14 to 25	18 to 32	17 to 23	23 to 31
> 25 to 32	19 to 24	16 to 17	21 to 23
> 32 to 50	15 to 23	14 to 16	19 to 21
> 50	< 18	< 14	< 19

**Estimated by the model for children to match the exposure of the average adult patient (70 kg) receiving rifapentine (900 mg) with food.*

Figure 3.3.3-3. Estimated rifapentine dosages for different age and body weight to reach target exposure in LTBI, latent tuberculosis infection, based on the Population PK model.



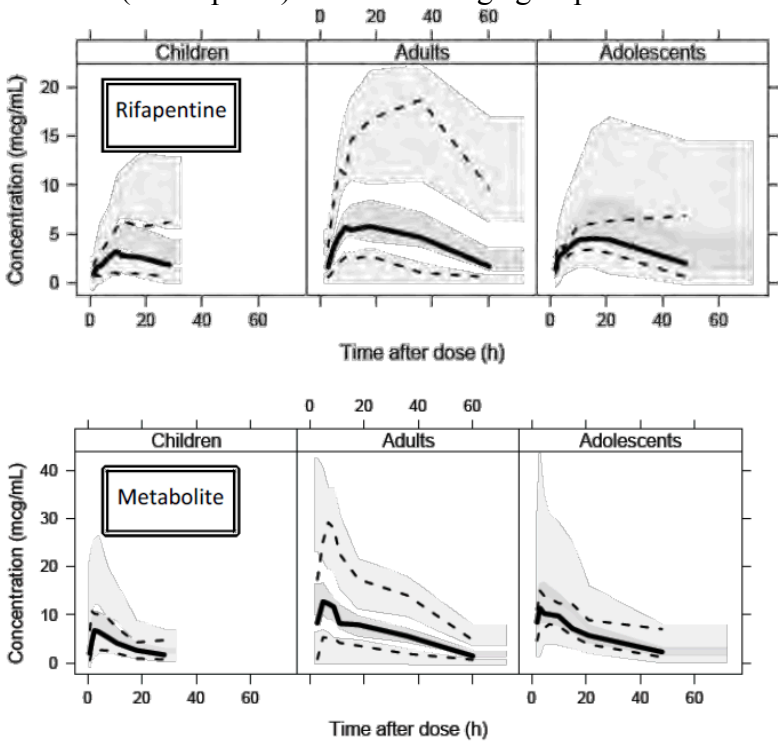




3.3.4 Model Evaluation

To evaluate whether the estimated fixed effect parameters adequately describe data, 1000 Monte Carlo simulation replicates of the original dataset were generated using each of the 3 key population PK models (Model I through Model III). The entire set of original observations in the original data was plotted versus time along with the summary statistics computed from the simulated data with 5th, 50th, and 95th percentiles. The Visual predictive check from the final joint model for both rifapentine and metabolite showed good agreement between observed and model predicted data for all age groups (**Figure 3.3.4-1**). The coincidence between the original data and simulated data demonstrated the predictive ability of fixed effects parameters in the final model. The visual predictive check was stratified on variables of interest such as study population. The goodness of fit plots for children, adults, and joint models are shown in **Figure 3.3.4-2, Figure 3.3.4-3,** and **Figure 3.3.4-4,** respectively**.**

Figure 3.3.4-1. Visual predictive check for blood levels of rifapentine (upper panel) and metabolite (lower panel) for different age groups.



Solid black line represents median of observed data. The dotted black lines are 5th and 95th percentile of the observed data. Middle grey shaded area represents simulated median with uncertainty (for 500 repetitions of visual predictive check). Lower and upper grey shaded areas represent simulated 5th and 95th percentile with uncertainty respectively.

Figure 3.3.4-2. Model Goodness of Fit and Validation for Children Final Model

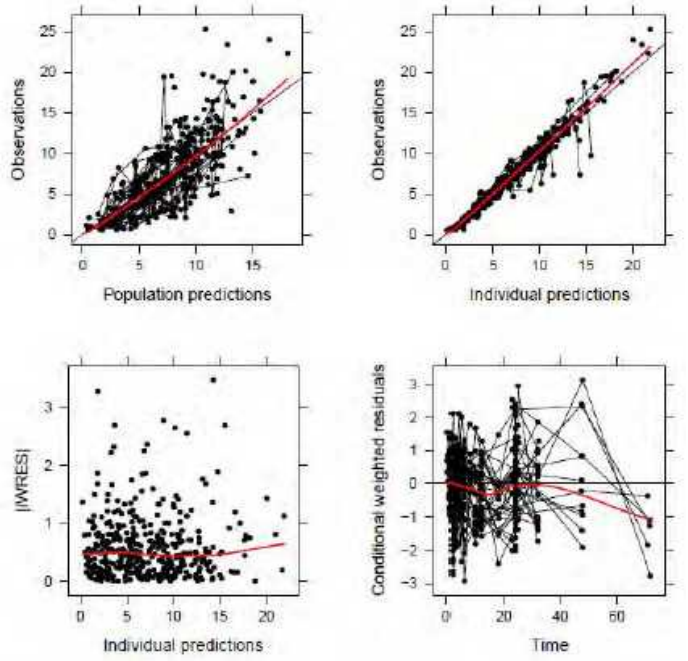


Figure 3.3.4-3. Model Goodness of Fit and Validation for Adults Final Model

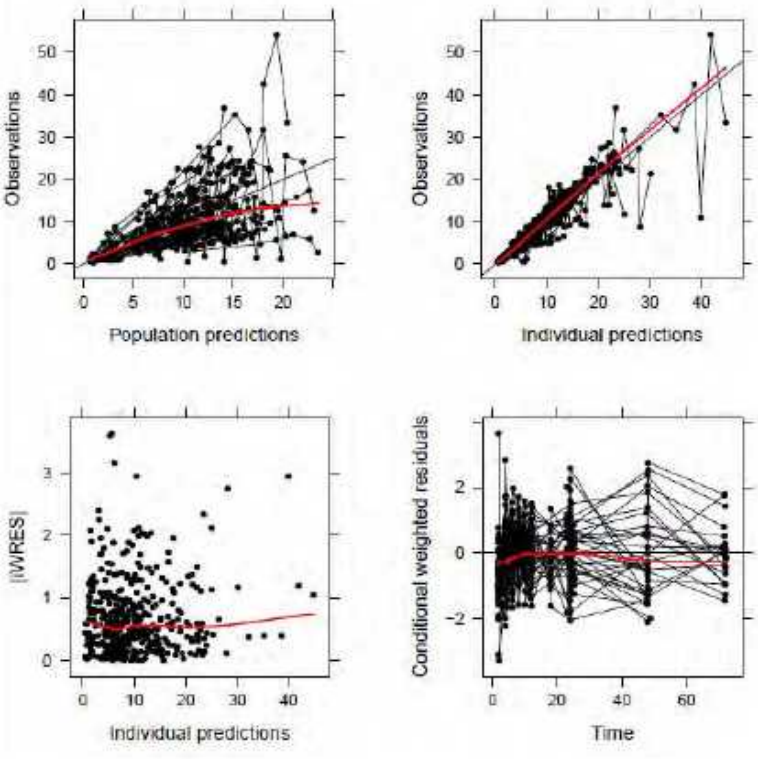
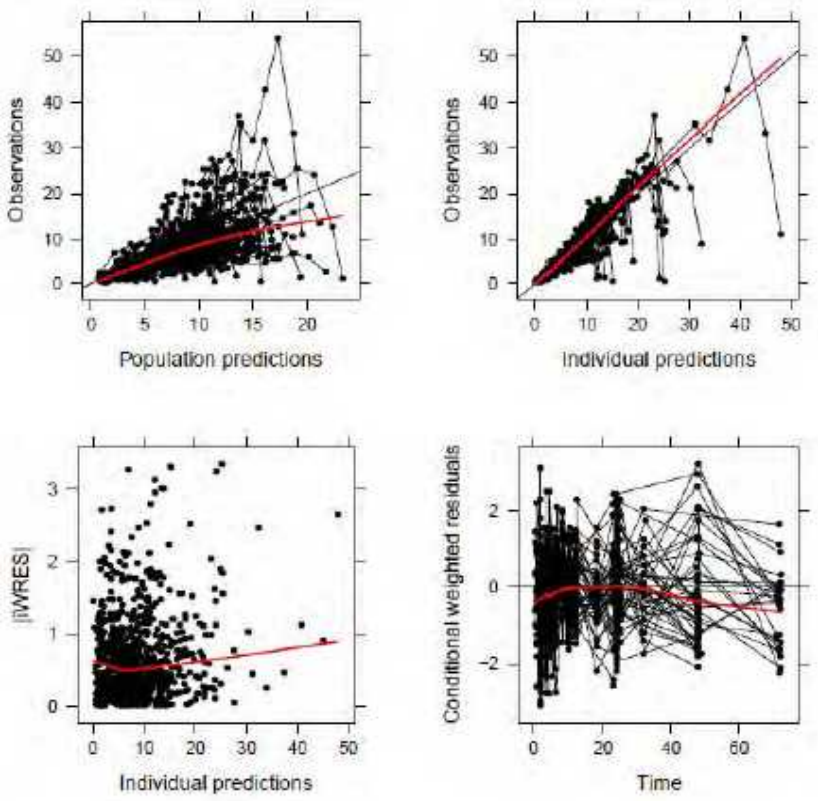


Figure 3.3.4-4. Model Goodness of Fit and Validation for Joint Final Model



Reviewer Comment: *The Goodness-of-fit plots indicate that the model reasonably describes both the available adult and pediatric data.*

3.3.5. Clinical Trial Simulation

A detailed overview of the clinical trial simulations focusing on % of adults and children being lower than 80% (efficacy) and higher than 120% (high exposure) of the target exposure are shown in **Table 3.3.5-1** and **Table 3.3.5-2**. The results are shown for each weight band, under fed and fast conditions and when tablet is given as whole and given as crushed. Target exposure is defined as median exposure in an adult population weighing 60-100 kg after ingestion of 900 mg tablet with food. Weight bands of 10-14 kg and 14-25 kg correspond to the age groups of 2-4 years and 4-9 years, respectively, while joined weight bands of 25-32 kg and 32-50 kg corresponds to pediatrics in the age group of 9-11 years.

The dosing algorithm used in the TBTC-S26 study produced somewhat higher rifapentine exposures in all children compared to adults. For children 10 to 14 kg, the proportion of children who achieved the target rifapentine exposures was similar with either the TBTC-S26 guideline or the population PK model guidelines (**Table 3.3.5-3**) when children received whole tablet with/without food. If children received TBTC-S26 dosages and tablet was crushed, then exposures in this group were lower compared to the target (**Table 3.3.5-1**). For children with weights greater than 14 kg, 87 to 90 percent of children achieved rifapentine exposures defined by an AUC greater than 80 percent of the geometric mean exposure in adults (**Table 3.3.5-3**). However, 16 to 20 percent of children are predicted to have AUC exposure exceeding the 5th percentile observed in adults (AUC>1264 mcg*h/L).

Table 3.3.5-1. Rifapentine AUC results for adults and children in fasten and fed conditions, after ingestion of whole/crushed tablet for each weight band

Weight band	Median AUC mcg*h/L	95% CI mcg*h/L	Median AUC mcg*h/L	95% CI mcg*h/L
	Food		Fast	
Adults, whole	627	283-1390	448	202-993
10-14 kg whole	694	327-1485	496	233-1061
10-14 kg crushed	515	242-1102	368	173-787
14-25 kg whole	867	390-1951	619	278-1393
14-25 kg crushed	643	290-1448	459	207-1034
25-32 kg whole	899	410-1951	642	292-1394
25-32 kg crushed	667	304-1448	477	217-1034
32-50 kg whole	939	419-2049	671	295-1464
32-50 kg crushed	697	311-1520	498	222-1086

Table 3.3.5-2. Percentages of population reaching rifapentine exposure lower than 80% and higher than 120% of the target exposure for each weight band. The results are shown under fast and fed conditions and when tablet is given as crushed and whole.

Weight Band	% of subject with AUC <0.8*target	% of subject with AUC >1.2*target	% of subject with AUC <0.8*target	% of subject with AUC >1.2*target
	Food		Fast	
Adults, whole	29	33	61	11
10-14 kg whole	23	40	53	14
10-14 kg crushed	49	17	79	4
14-25 kg whole	9	62	32	30
14-25 kg crushed	28	34	60	11
25-32 kg whole	7	65	28	32
25-32 kg crushed	25	36	57	12
32-50 kg whole	7	68	27	35
32-50 kg crushed	23	39	54	13

Table 3.3.5-3. Comparison of different rifapentine dosing algorithms in children.

Algorithm	Dose	Dosage (mg/kg)	Proportion of children with AUC>80% of adult AUC (%) [70% Expected]	Proportion of children having high AUC (%) (corresponding to the upper adult tail (5th percentile)) [5 % expected]
PREVENT TB	300	21-30	71.6	5
Modeled	266-342	21-27	71.9	5
Modeled with 150mg tablet	300	21-30	71.6	5
High modeled	400-513	31-40	95	22
PREVENT TB	450	18-32	87	16
Modeled	290-450	17-24	71	5
Modeled with 150mg tablet	300,450	14-27	71	5
High modeled	436-667	25-37	94	28
PREVENT TB	600	19-24	89	16
Modeled	422-516	16-18	72	5
Modeled with 150mg tablet	450	14-18	72	5
High modeled	436-667	24-27	94	20
PREVENT TB	750	15-23	90	20
Modeled	505-707	14-16	71	5
Modeled with 150mg tablet	450,600,750	13-18	71	5
High modeled	760-1060	21-24	95	28

**PREVENT TB is the dosing algorithm used in the Phase 3 clinical trial and PK substudy.*
***Modeled is an algorithm estimated by the model as if a liquid formulation was available assuming same bioavailability between liquid formulation and tablet in either fast or fed condition, where food condition in adults used to compute reference AUC value matches food condition.in children*
****Modeled with 150mg tablet is an algorithm estimated by the model using current 150 mg tablet formulation assuming the table is given as whole.*
*****High modeled is an algorithm estimated by the model to ensure that 95% of the children will achieve at least 80% of the adult exposure when taking whole tablet*

3.4 Highlight s of Sponsor's Conclusions

- Rifapentine clearance scaled for size was higher in children than in adults. There was an additional increase in clearance per kilogram body weight of 21% for the youngest child (age, 2 y) compared with that expected from allometric scaling. This difference disappeared with increased age, with an estimated half-life of 1.5 years, and allometric scaling was sufficient to explain the relation between clearance and growth in children aged ≥ 9 years.

- Age and body weight were important covariates in rifapentine clearance, with the predominant impact of age observed for pediatric patients with age <6 years.
- Food increased rifapentine bioavailability by 40%.
- Crushing rifapentine tablets caused 26% decrease in bioavailability.

4 Reviewer's Analysis

4.1 Objectives

Based on the high correlation between rifapentine concentrations at 24 hours post-dose (C_{24}) and AUC observed in previous studies, the reviewer conducted independent analyses for the following objectives:

1) To compare the observed rifapentine C_{24} between children (among different weight bands) and adults
2) To evaluate the effect of food, and tablet integrity on rifapentine C_{24}
3) To compare results derived from observed rifapentine C_{24} and from model predicted AUC

4.2 Methods

4.2.1 Data Sets

Data Sets used in the Reviewer's analysis are summarized in **Table 4.2.1-1**. Data from TBTC Study 26 were extracted and rifapentine concentrations (C_{24}) determined in this study were used for Reviewer's analysis.

Table 4.2.1-1. Analysis Data Sets

Study Number	Name	Link to EDR
Population PK TBTC Studies 25, 26, adolescent, and Children study	final.xpt	\\cdsesub1\evsprod\NDA021024\0016\m5\datasets\tbtc-s26-pk-substudy\analysis\legacy\datasets

4.2.2 Software

Statistical summaries and plotting were performed using R version 3.1.0.

4.3 Results

As shown in **Table 4.3-1**, model predicted rifapentine geometric mean AUC was 31% higher in children compared to adults (720 vs. 551 µg*h/mL, P<0.0001). The geometric mean AUC in children administered crushed rifapentine tablets was lower than in children administered whole tablets (656 vs. 884 µg*h/mL, respectively, P=0.0004) but still significantly higher than in adults (P=0.005). Relative to rifapentine AUC in adults, model predicted rifapentine geometric mean AUC was 60% and 19% higher in children administered whole tablets and in children administered crushed tablets, respectively. Similar to AUC, the observed C_{24} were 28%, 66%, and 14% higher in all children (p=0.002), in children administered whole tablets (p<0.0001) and crushed tablets (p=0.13; although not statistically significant) than in adults receiving 900 mg tablets. The observed geometric mean rifapentine C_{24} was significantly greater with whole vs.

crushed tablets in children (p=0.001). The ratios of geometric mean AUC and C_{24} of 25-desacetyl rifapentine were similar to rifapentine in children and adults (**Table 4.3-1**).

Table 4.3-1. Model Predicted AUC and Observed C_{24} of Rifapentine and 25-Desacetyl Rifapentine by Tablet Integrity

Rifapentine	**Children**			**Adult N=77**
	All children N=80	**Whole Tablet N=25**	**Crushed Tablet N=55**	
Model Predicted AUC (µg*h/mL)				
Geometric Mean	720	884	656	551
CV%	38	26	39	36
Geometric Mean Ratio (vs. Adults) *p*-value (vs. Adults)*	1.31 <0.0001	1.60 <0.0001	1.19 0.005 {0.0004†}	N.A.
Observed C_{24} (µg/mL)				
Geometric Mean	10.9	14.1	9.7	8.5
CV%	57	33	61	48
Geometric Mean Ratio (vs. Adults) *P*-value (vs. Adults)*	1.28 0.002	1.66 <0.0001	1.14 0.16 {0.001†}	Not Applicable
25-Desacetyl Rifapentine	**Children**			**Adult N=77**
	All children N=80	**Whole Tablet N=25**	**Crushed Tablet N=55**	
Model Predicted AUC (µg*h/mL)				
Geometric Mean	735	843	691	521
CV%	54	36	60	48
Geometric Mean Ratio (vs. Adults) *p*-value (vs. Adults)*	1.41 <0.0001	1.62 <0.0001	1.33 0.011 {0.0085†}	Not Applicable

Observed C_{24} (µg/mL)				
Geometric Mean	15.1	17.9	13.9	10.4
CV%	63	41	70	0.48
Geometric Mean Ratio (vs. Adults) *P*-value (vs. Adults)*	1.45 <0.0001	1.72 <0.0001	1.34 0.005 {0.006†}	Not Applicable

Note: AUC and C_{24} data are extracted from Sponsor's report of TBTC Study 26 PK, Table S11. Results from Reviewer's analysis on C_{24} agree with those from Sponsor's analysis.
**P-value based on t-test on $\log_e$ transformed data in comparison of all children vs. adults and by Fisher's LSD in each children group (whole or crushed tablet) vs. adults. † P-value by Fisher's LSD for comparison between children administered whole vs. crushed rifapentine tablets.*

In a separate analysis of patients who received the correct rifapentine dose based on weight band, both rifapentine model predicted AUC and observed C_{24} were higher in the 14.1-25.0 kg, 25.1-32.0 kg, and 32.1-50.0 kg weight band compared to the >50 kg weight band and the 10.0-14.0 kg weight band (**Tables 4.3-2 and 4.3-3**). The 10.0-14.0 kg weight band was comprised of 13 children, all of whom received crushed tablets and presented with the lowest exposure (both AUC and C_{24}). The lower weight bands (10.0-14.0 kg and 14.1-25.0 kg) received a higher geometric mean doses based on mg/kg (23.6 mg/kg and 25.3 mg/kg, respectively) compared to the highest weight band (>50 kg: 10.8 mg/kg). In contrast, the geometric mean AUC of 25-desacetyl-rifapentine in all children weight bands was higher than that in adults regardless of tablet integrity (**Table 4.3-4**). Moderate inter-patient variations in AUC and C_{24} were observed in all weight bands except in the lowest weight band (10-14.0 kg) where higher inter-patient variations (>50%) AUC and C_{24} were observed (**Tables 4.3-2 and 4.3-3 and Figures 4.3-1 and 4.3-2**). In addition, rifapentine exposures (both AUC and C_{24}) were higher in 14.1-25.0 kg, 25.1-32.0 kg, and 32.1-50.0 kg administered whole tablets compared to crushed tablets (**Figures 4.3-1 and 4.3-2**).

Table 4.3-2. Model Predicted RPT AUC by Weight Band and Tablet Integrity (Crushed or Whole) (Sponsor's Analysis; adapted from Sponsor's report of TBTC Study 26 PK, Table S13)

						RPT AUC (mcg*h/mL)						
Weight Band (kg)	**Age Group**	**RPT Dose (mg)**	**N**	**Tablet Integrity**	**Geometric Mean of RPT mg/kg[a]**	**Geometric Mean RPT AUC (90% CI)**	**CV**	**Min**	**25th Percentile**	**Median**	**75th Percentile**	**Max**
10.0-14.0	Child	300	13	Crushed	23.6	504 (399-637)	0.5	184.7	375.7	489.9	706.5	989.3
14.1-25.0	Child	450	26	Crushed	25.3	744 (684-810)	0.32	365.7	584.4	765.9	968.1	1301.4
		450	13	Whole								
25.1-32.0	Child	600	4	Crushed	21.3	762 (558-1041)	0.34	545	637.4	746.5	765.5	1297
		600	1	Whole								
32.1-50.0	Adult	750	1	Whole	18.7	813 (721-916)	0.28	539.5	615.6	883.9	1022.4	1184.2
	Child	750	8	Crushed								
		750	7	Whole								
>50	Adult	900	76	Whole	10.8	551 (517-588)	0.35	263.6	440.1	554.6	733.5	1300.7
	Child	900	1	Crushed								
		900	2	Whole								

Note: Table based on those participants who received the correct RPT dose for their weight band. Children that did not receive the correct RPT dose based on their weight band were removed. These include: 1 child in weight band 10.0-14.0 kg who received RPT 450 mg; 1 child in weight band 14.1-25.0 kg who received RPT 600 mg; 2 children in weight band 25.1-32.0 kg, where 1 received RPT 450 mg and the other received RPT 750 mg; and 1 child in weight band 32.1-50.0 kg who received RPT 600 mg.
[a]Geometric Mean RPT mg/kg by RPT dose.

Table 4.3-3. Observed RPT C_{24} by Weight Band and Tablet Integrity (Crushed or Whole) (Reviewer's Analysis)

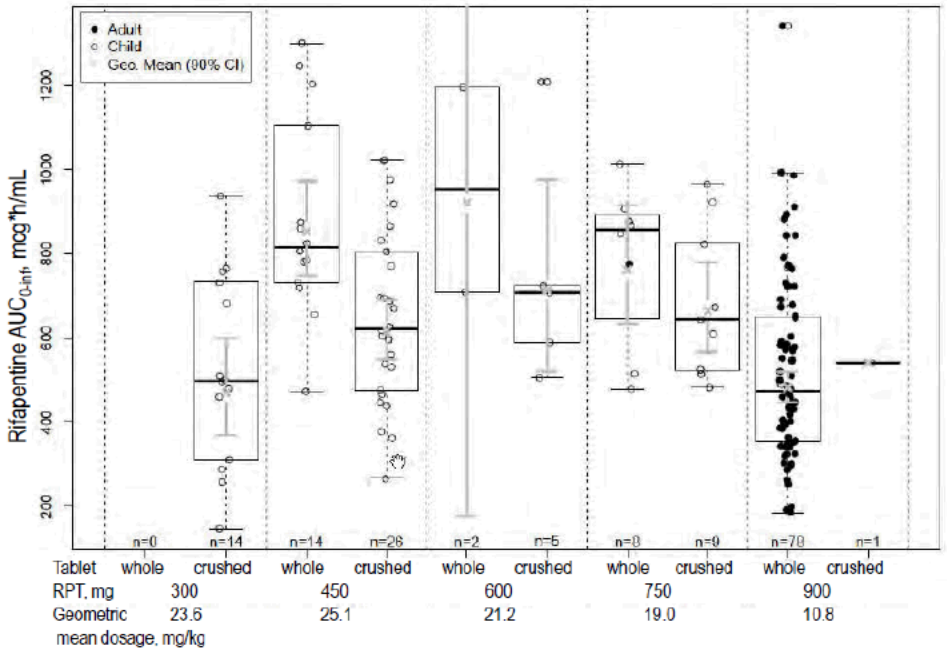
Weight Band (kg)	Age Group	RPT Dose (mg)	N	Tablet Integrity	Geometric Mean of RPT mg/kg	RPT C_{24} (µg/mL)						
						Geometric Mean	CV	Min	25th Percentile	Median	75th Percentile	Max
10.0-14.0	Child	300	13	Crushed	23.6	6.4	0.88	1.4	3.7	7.2	11.9	18.1
14.1-25.0	Child	450	26	Crushed	25.3	11.3	0.47	3.0	9.3	12.8	14.2	23.4
			13	Whole								
25.1-32.0	Child	600	3	Crushed	21.3	14.0	0.43	9.6	11.6	12.6	16.1	25.3
			1	Whole								
32.1-50.0	Adult	750	1	Whole	18.7	13.0	0.31	8.0	8.3	13.4	16.6	19.4
	Child		8	Crushed								
			7	Whole								
>50	Adult	900	76	Whole	10.8	8.5	0.48	2.9	4.4	8.4	11.9	27.7
	Child		1	Crushed								
			2	Whole								

Table 4.3-4. Model Predicted 25-Desacetyl-Rifapentine AUC by Weight Band and Tablet Integrity (Crushed or Whole) (Sponsor's Analysis; adapted from Sponsor's report of TBTC Study 26 PK, Table S13)

Weight Band (kg)	Age Group	RPT Dose (mg)	N	Tablet Integrity	Geometric Mean of RPT mg/kg[a]	25-Desacetyl-Rifapentine AUC (mcg*h/mL)						
						Geometric Mean RPT AUC (90% CI)	CV	Min	25th Percentile	Median	75th Percentile	Max
10.0-14.0	Child	300	13	Crushed	23.6	566 (405-792)	0.76	139.6	458.8	516.3	985.6	1320.7
14.1-25.0	Child	450	26	Crushed	25.3	745 (650-852)	0.53	273.4	489.2	815.3	1052.4	2018.7
		450	13	Whole								
25.1-32.0	Child	600	4	Crushed	21.3	732 (494-1084)	0.43	554.9	601.7	612.4	680.4	1511.6
		600	1	Whole								
32.1-50.0	Adult	750	1	Whole	18.7	861 (720-1028)	0.42	414.4	673.3	940.8	1189.4	1444.7
	Child	750	8	Crushed								
		750	7	Whole								
>50	Adult	900	76	Whole	10.8	520 (479-566)	0.47	187.9	380.3	514.6	701.3	1427.5
	Child	900	1	Crushed								
		900	2	Whole								

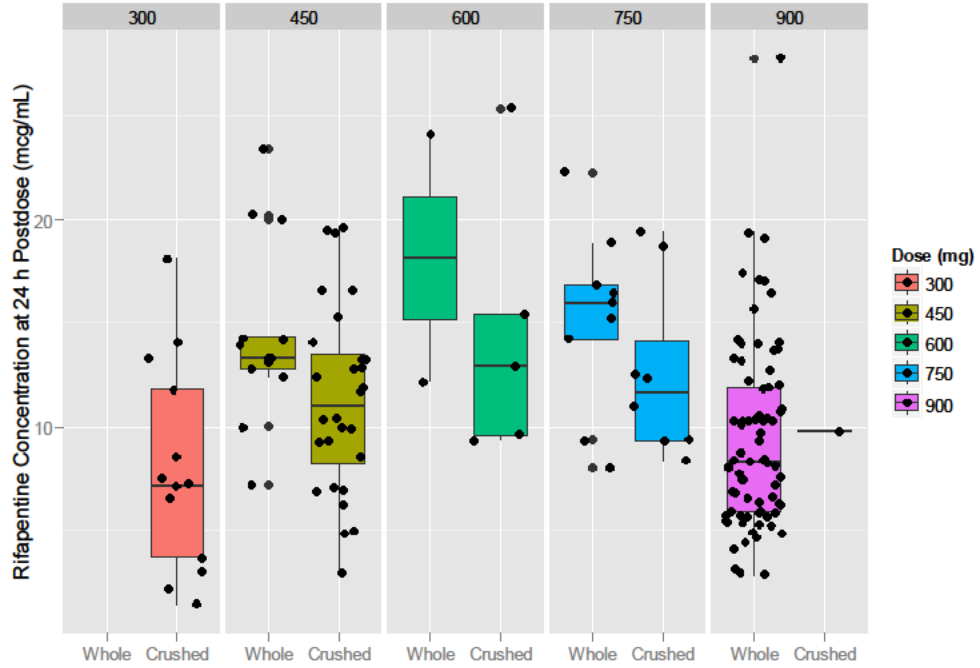
Abbreviations: RPT=rifapentine; AUC=area under the concentration-time curve; Min=minimum; Max=maximum; N=number [of patients]; CI=confidence interval; CV=coefficient of variation
Note: Table based on those participants who received the correct RPT dose for their weight band. Children that did not receive the correct RPT dose based on their weight band were removed. These include: 1 child in weight band 10.0-14.0 kg who received RPT 450 mg; 1 child in weight band 14.1-25.0 kg who received RPT 600 mg; 2 children in weight band 25.1-32.0 kg, where 1 received RPT 450 mg and the other received RPT 750 mg; and 1 child in weight band 32.1-50.0 kg who received RPT 600 mg. Data for all patients are included in Table 14.5.2.
[a]Geometric Mean RPT mg/kg by RPT dose.

Figure 4.3-1. Rifapentine AUC by Rifapentine Dose (mg) and Tablet Integrity (Crushed or Whole) (Sponsor's analysis)



Box plots of RPT AUC0-inf vs. groups of patients split (1) by the rifapentine dose (mg) used in the treatment algorithm and (2) by RPT tablet integrity (crushed or whole). The 25th, 50th, and 75th percentiles are indicated by the bottom, middle, and top of the box plots, respectively, and the whiskers are drawn at either the maximum (minimum) or 1.5 times the IQR above (below) the 75th (25th) percentile depending on which of the 2 is closer to the median. The geometric means (X) and 90% CIs are indicated for each group.

Figure 4.3-2. Observed Rifapentine C_{24} by Rifapentine Dose (mg) and Tablet Integrity (Crushed or Whole) (Reviewer's analysis)



As shown in shown in **Tables 4.4-5 and 4.4-6**, food increased rifapentine exposures (AUC and C_{24}) in both children (by 25-30%) and adults (by ~40%), although the difference in rifapentine AUC and C_{24} with or without food was not statistically significant for children (P>0.05) due to small sample size (n=10) and large inter-subject variability in children administered rifapentine without food.

Table 4.4-5. Comparisons of Model Predicted Rifapentine AUC in Both Children and Adults When Administered With and Without Food (Sponsor's analysis; adapted from Sponsor's report of TBTC Study 26 PK, Table S18)

Population	N	Geometric Mean RPT AUC (mcg*h/mL)	CV	Min	Max	90% CI	*P*-value*
Child with Food	70	740.3	0.34	283.0	1333.7	(693.1, 790.8)	0.23
Child with no Food	10	590.2	0.59	184.7	1095.5	(430.5, 809.0)	
Adult with Food	53	613.8	0.33	273.7	1300.7	(570.2, 660.8)	<0.0001
Adult with no Food	24	434.3	0.29	263.6	847.2	(393.3, 479.6)	

**P-value based on t-test using lognormal transformation.*
Abbreviations: AUC=area under the concentration time curve; CI=confidence interval; Min=minimum; Max=maximum; N=number; CV=coefficient of variation; RPT=rifapentine; PK=pharmacokinetic.

Table 4.4-6. Comparisons of Observed Rifapentine C_{24} in Both Children and Adults When Administered With and Without Food (Reviewer's analysis)

Population	N	Geometric Mean RPT C_{24} (µg/mL)	CV	Min	Max	90% CI	*P*-value
Child with Food	70	11.3	0.51	2.2	25.3	(11.0, 11.6)	0.33
Child without Food	10	8.7	0.93	1.4	19.5	(7.4, 9.9)	
Adult with Food	53	9.5	0.47	2.9	27.7	(9.1, 9.8)	0.0016
Adult without Food	24	6.7	0.42	3.0	17.0	(6.2, 7.3)	

***Overall Reviewer's Comment for Population PK Analysis**: Previous studies showed that rifapentine concentrations at 24 hours post-dose (C_{24}) correlated well with rifapentine exposure (AUC); therefore, a separate analysis was conducted by the Reviewer to compare the observed C_{24} between children (among different weight bands) and adults, and to evaluate the effects of food and tablet integrity on rifapentine C_{24}. The results derived from observed rifapentine C_{24} agree with those derived from AUC predicted by the population PK model, which suggests that the population PK model developed by the Sponsor is able to describe adequately rifapentine PK in children and adults.*

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/s/

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