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ORIGINAL RESEARCH ARTICLE

Bridging to Paediatric Dosing: Relative Bioavailability of Suspended Rifapentine and Isoniazid in an Open-Label Randomized Trial in Adults on Tuberculosis Preventive Therapy

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Abstract

Background and Objectives The use of the 12-dose, once-weekly, rifapentine-based (3HP), short-course tuberculosis preventive treatment (TPT) in children has been limited due to a lack of child-friendly rifapentine formulations. In this study, we compared the relative bioavailability of rifapentine and isoniazid when suspended in water versus whole tablets, using generic adult formulations.

Methods We assessed the relative bioavailability of non-dispersible rifapentine and isoniazid adult tablets suspended in water compared with whole tablets. Adults with a positive tuberculosis infection test were randomized 1:1:1 to receive two of three rifapentine/isoniazid formulations in separate treatment sequences, including two generic brands of fixed-dose combinations and standalone tablets of rifapentine and isoniazid. Participants received either whole tablets swallowed or tablets suspended in water at a dose of 900 mg for each drug once weekly over 12 weeks with intensive pharmacokinetic sampling up to 48 h post-dose. Nonlinear mixed-effects modelling was used to compare the relative bioavailability of suspended versus whole tablets, with 90% confidence intervals (CI) evaluated against the standard bioequivalence range (80–125%).

Results In 24 participants, a one-compartment model described rifapentine data well. A two-compartment model with a mixture component for fast/intermediate and slow acetylators best described isoniazid. Rifapentine and isoniazid demonstrated similar bioavailability across all dosing forms, meeting formal bioequivalence criteria. The absorption rates for suspended tablets were faster than those for whole tablets by 22.2% (90% CI 12.4–30.8) for rifapentine and 35% (90% CI 26.1–42.6) for isoniazid.

Conclusion Both rifapentine and isoniazid, whether in fixed-dose combinations or as standalone, showed similar bioavailability when administered as whole tablets or suspended in water. These findings support dosing in children and other populations without the need to adjust rifapentine or isoniazid doses, thereby supporting broader access to the 3HP regimen.

Pan African Clinical Trials Registry PACTR202306775627089, registration date June 15, 2023.

1 Introduction

Tuberculosis (TB) remains a leading cause of morbidity and mortality globally. Children below 15 years of age accounted for approximately 12% of the total number of new TB cases in 2023, with approximately one million children developing TB each year, contributing to a disproportionate 16% of TB-related deaths [1]. Paediatric TB is preventable, and treatment outcomes are good when children are diagnosed and treated appropriately. Children with TB exposure are at high risk of progression to disease and severe forms of disease, with the highest risk occurring in children younger than 5 years, a positive test of TB infection, those living with HIV and those with malnutrition [2–4].

TB preventive treatment (TPT) significantly reduces the risk of progression to TB disease in children, adolescents and adults and is recommended in people living with HIV, household contacts of people diagnosed with pulmonary TB and other clinical risk groups [5]. Several TPT regimens are recommended for children by the World Health Organization (WHO), including 6 months of daily isoniazid (6H), 3 months of rifampicin and isoniazid (3HR), 3 months of

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Key Points

This study addresses the critical need for evidence confirming that suspending adult formulations for paediatric dosing of rifapentine and isoniazid does not compromise drug exposure or safety.

Our findings show similar bioavailability of suspended formulations of rifapentine and isoniazid compared to whole tablets. This means that no dose adjustment is required when adult tablets are suspended—an approach that could significantly enhance access to rifapentine-based regimens for young children.

once-weekly rifapentine and isoniazid (3HP) and 4 months of rifampicin (4R) [5]. Implementation of TPT remains challenging: 2.2 million household child contacts younger than 5 years started TPT (55% of the targeted 4 million) between 2018 and 2022; for contacts older than 5 years, this figure was only 10% (2 million of the targeted 20 million) [6]. Long TPT regimens remain a significant barrier to TPT completion, with < 20% completing 6 months of TPT in routine care [7].

The completion of TPT in children may be improved by better access to short courses and child-friendly regimens [8]. Given its relative safety, higher completion rates and short duration, the 3HP regimen, 12 once-weekly doses of rifapentine and isoniazid, is an attractive option. Although the TB Trials Consortium Study 26, a phase III trial, excluded children under 2 years of age, 3HP is safe and effective for children of all ages and is currently recommended by the WHO [4, 8]. Globally, access to 3HP in children and adults has been hampered by the lack of access to affordable and child-friendly rifapentine formulations. Several generic drug companies have developed rifapentine standalone or fixed-dose combinations (FDCs) for use in adults which are WHO prequalified and are globally available. Child-friendly dispersible formulations of isoniazid and rifapentine are now available and should be prioritized for use in children. However, global scale-up may take time, and these formulations are not yet accessible in all regions. In such cases, using widely available adult formulations could help reduce barriers to 3HP access for children in the field.

We assessed the pharmacokinetics (PK) of rifapentine and isoniazid, focusing on their relative bioavailability and absorption profiles when taken as whole tablets or suspended in water. Additionally, we assessed the safety of the respective formulations and administration methods.

2 Methods

2.1 Study Design

This randomized, open-label crossover trial was performed at a single centre in Cape Town, South Africa (TASK Clinical Research Centre, Bellville). The pharmacokinetics, palatability and safety of rifapentine and isoniazid administered suspended in water versus whole tablets were assessed for two generic fixed-dose combinations (MacLeods, India [brand 1] and Lupin, India [brand 2]) and standalone tablets (rifapentine, Lupin, India and isoniazid, Winthrop, India).

2.2 Study Population

Adults aged 18–55 years with a body weight between 40 kg and 90 kg, who had documented recent household contact with a patient newly diagnosed with drug-susceptible pulmonary TB in the past 12 months, were recruited. After obtaining informed consent, an interferon-γ release assay was performed, and participants were screened for active TB (exclusion criterion) using a symptom questionnaire, physical examination, chest radiograph (AP and lateral), and sputum testing (Gene-Xpert MTB/RIF Ultra, Cepheid). Other exclusion criteria were pregnancy, HIV or chronic hepatitis B infection, completion of TPT within the past 12 months, substance or alcohol abuse, or any contra-indications to rifapentine or isoniazid, including co-medications with significant interactions with rifapentine.

Participants were randomly assigned 1:1:1 to receive two of the three study products (or combinations of products) in two independent treatment sequences to first receive the suspended or the whole form of the respective tablets (Fig. 1).

The planned sample size was 24 participants, resulting in 16 participants on each respective formulation due to the crossover design, with both dosing events (whole and suspended tablets). Clinical trial simulations in NONMEM showed that with this sample size, the power to detect a 20% decrease in bioavailability on a 95% confidence interval (CI) was estimated at 93.9%, with an expected type I error rate of 2.6%.

2.3 Preparation and Administration of Tablets

The suspended and whole formulations were prepared by study pharmacists. For the first four weekly doses, when PK sampling was completed, treatment was administered 30 min after a standardized breakfast (670 kcal, approximately 33% fat) with 100 mL of distilled water. If treatment was required to be suspended, the film-coated tablets were cut in quarters and crushed to powder inside the same container used as a

dosing cup to prevent any powder wastage. The suspension itself was prepared by study nurses a maximum of 5 min prior to dosing. Thirty millilitres of distilled water was added to the crushed tablets, and the container was swirled for a minimum of 20 s. After administration, the container was rinsed with the remaining 70 mL of distilled water, which was thereafter also administered to the participant. In the case of dosing of whole tablets, these were also taken with 100 mL distilled water.

2.4 Pharmacokinetic Sample Collection

Sampling was performed starting on days 1, 8, 15 and 22 from just before, and 1, 2, 3, 4, 5, 6, 8, 24 and 48 h after administration of study drugs. A single sample was drawn on day 29 (168 h after the 4th dose). At each time point, 2 mL of blood was drawn in a K2-EDTA tube and placed on ice immediately. Samples were centrifuged at 1500 G for 10 min at 4 °C. Plasma was stored within 1 h of sample collection at − 80 °C until analysis at the Division of Clinical Pharmacology, University of Cape Town using previously published assay methods [9]. Plasma samples were analysed with validated liquid chromatography-tandem mass spectrometry. The lower limit of quantification (LLOQ) for rifapentine was 0.0781 µg/mL and 0.105 µg/mL for isoniazid.

2.5 Population Pharmacokinetic Model Development

A population PK model for rifapentine developed by Hibma et al. was used as the base model structure. This model includes one disposition compartment for rifapentine, with first-order absorption through transit compartments, and an enzyme turnover model to describe rifapentine autoinduction [10]. For isoniazid, the base model structure was adapted from the population PK model by van Beek et al., which features a two-compartment model with first-order absorption via a four-transit compartment model into a well-stirred liver compartment, followed by first-order elimination [11]. The metabolite components of the model structures were discarded due to the absence of sample data for 25-diacetyl-rifapentine and acetyl-isoniazid. Inter-individual variability (IIV) and inter-occasional variability were modelled using

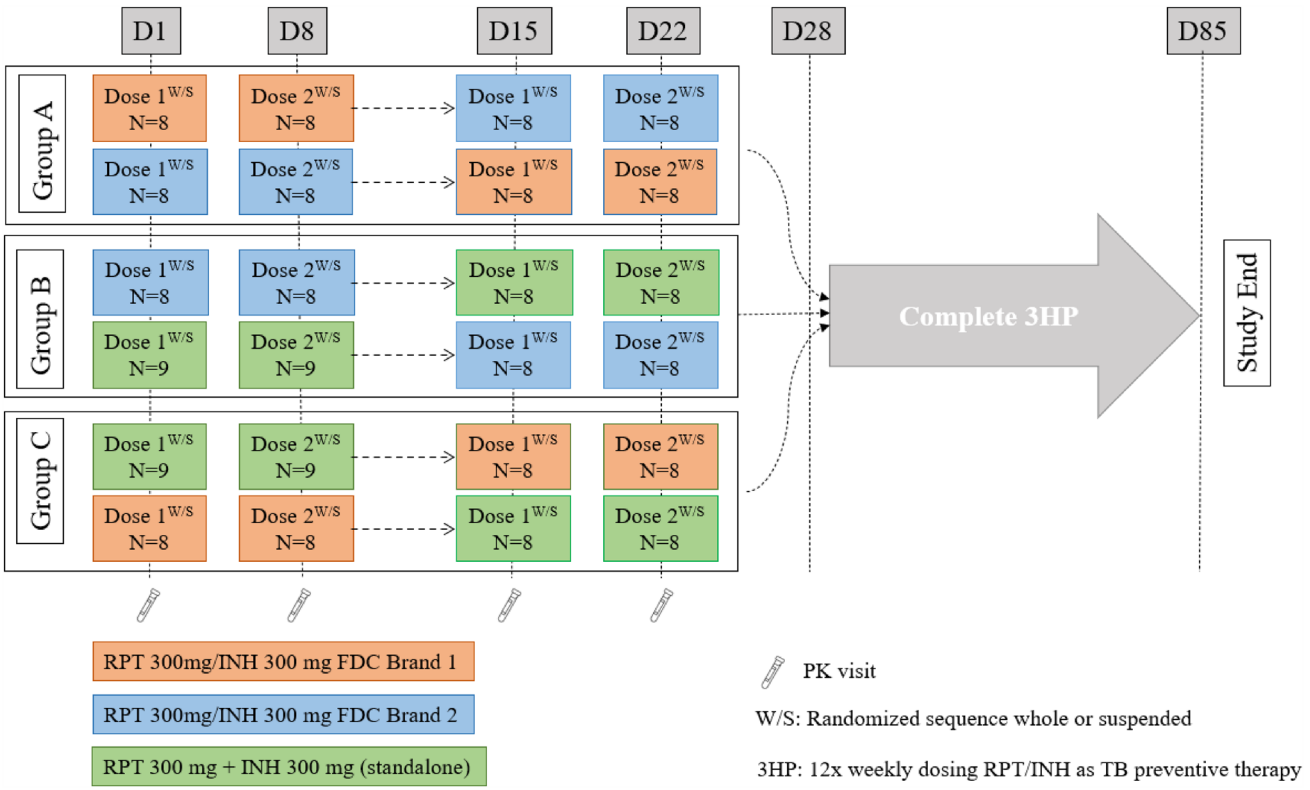

Fig. 1 Study design and overview of trial schema. Formulations: Fixed-dose RPT 300 mg/INH 300 mg (Brand 1 [Orange], Brand 2 [Blue]); standalone RPT 300 mg combined with standalone INH 300 mg (Green). *3HP* 12 weekly doses of RPT/INH for TB prevention, *D* day, *FDC* fixed dose combination, *INH* isoniazid, *RPT* rifapentine, = PK visits, *W/S* randomized sequence (whole or suspended)

log-normal distributions. Residual unexplained variability was assessed using additive, proportional, and combined additive and proportional models. Allometric scaling was tested on clearance (CL) using an exponent of 0.75 and on the volume of distribution (V) with an exponent of 1 based on body weight or calculated fat-free mass [12]. The effect of study products as suspended in water compared with a whole tablet was evaluated and parameterized on bioavailability (F) and mean transit time (MTT) as Eq. 1:

$$P_{i,j} = \theta_{ij} \times (1 + \theta_{ij}\text{suspension effect}) \quad (1)$$

where P is the tested parameter, i represents either rifapentine or isoniazid, j represents the FDC brand 1, FDC brand 2, and the standalone whole tablet of each study drug, which was used as the reference, with $\theta = 1$.

The effect of the formulation was also tested on the variability of the absorption rate and relative bioavailability in a proportional relationship.

First-order conditional estimation with interaction (FOCE-I) was used for parameter estimation. Model selection and evaluation were conducted using log-likelihood ratio tests, incorporating objective function value (OFV, $-2 \times \log$(total likelihood of data)), goodness-of-fit plots, visual predictive checks (VPCs) and scientific plausibility. The significance of differences in model fit for nested models was assessed using a χ^2 test with a p-value < 0.05. Parameter uncertainty was estimated using sampling importance resampling (SIR) [13]. According to the European Medicines Agency (EMA) bioequivalence guidelines, the estimated 90% CI for the potential effect of formulation or brand on bioavailability was evaluated. To meet the bioequivalence criterion, the 90% CI is required to fall within 80–125% of the reference product's bioavailability [14]. A log-likelihood profiling (LLP) approach was used to obtain the 90% CIs for bioavailability and absorption rate differences between formulations [15].

Noncompartmental analysis (NCA) was performed to obtain the secondary PK parameters, including $AUC_{0-168\ h}$ for rifapentine and $AUC_{0-24\ h}$ for isoniazid, maximal plasma concentration (C_{max}), and time to maximal plasma concentration (T_{max}). Simulation-based posterior predictive checks (PPC) for the final population PK (PopPK) model, based on NCA metrics, were conducted using 1000 simulated datasets to evaluate the model's performance. The mean AUC of each simulated dataset was calculated. The NCA-PPC analyses were performed using the ncappc tool [16].

The modelling and simulation procedures were conducted using NONMEM 7.5, supported by Perl-speaks-NONMEM (PsN) 5.3.0 (http://psn.sourceforge.net) [17]. R software was utilized for data management, graphical analysis, model diagnostics, and statistical summaries, with the R packages Xpose (http://xpose.sourceforge.net), ggplot2, and ncappc [16, 18]. Pirana software version 24.9.2 was used to handle model output and summary [19]. The analysis was performed on the Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX) cluster using a Linux operating system.

2.6 Safety

Safety was monitored from the first dose of rifapentine/isoniazid until the final follow-up visit of the study. The severity and attribution of adverse events were graded according to the DAIDS Regulatory Support Centre as defined in the Adverse Events Grading Tables (Version 2.1, July 2017).

3 Results

3.1 Demographics and Safety

A total of 24 participants were included in the final analysis after two early withdrawals, both occurring after two doses of the study medication. One withdrawal was due to a serious adverse event of optic neuritis, while the other was related to socio-behavioural issues. The demographic of the study population is summarized in Table 1.

There were 58 treatment-emergent adverse events (TEAE) reported in 22 participants with no clear correlation to respective formulations or administration methods (Supplementary Table 1, see Electronic Supplementary Material [ESM]). The majority were mild (91.4%) to moderate (6.9%). Five events were possibly related to the study treatment (constipation, nausea, rash, decreased appetite and dizziness, respectively). One serious adverse event (SAE) led to study withdrawal due to decreased vision, where the participant was diagnosed with optic neuritis after two doses of study treatment (suspended rifapentine and isoniazid standalone). This SAE was deemed unlikely to be related to the study treatment as assessed by an independent neurologist. The participant was treated with corticosteroids, and her complaints improved. Six participants developed elevated γ-glutamyl transferase (GGT) levels, with a maximum of 170 U/L on day 11. Alanine aminotransferase (ALT) was elevated in two individuals, with a maximum value of 51 U/L. No participants experienced any other clinically significant changes in safety laboratory tests during the study.

3.2 Population Pharmacokinetic Modelling Results

A total of 838 observations of rifapentine and 707 of isoniazid from 24 participants were available for the analysis. Summarized observed concentrations of rifapentine and isoniazid are shown in Fig. 2. Among rifapentine

Table 1 Demographics characteristics of the study population

Characteristic	Value
Sex	
Male	4 (16.7)
Female	20 (83.3)
Race	
Mixed race	22 (91.7)
Black	2 (8.3)
Age (years)	37.5 (26.5–45.3)
Weight (kg)	61.1 (51.1–66)
Height (m)	1.59 (1.56–1.65)
Body mass index (kg/m^2)	22.4 (20.2–27.5)
Fat-free mass (kg)	38.6 (34.5–42.8)

Values are presented as *n* (%) for categorical variables and median (interquartile range) for continuous variables

BMI body mass index, *kg* kilogram, *m* meter

samples collected 0–48 h post-dose, 3.0% (26/864) were below the limit of quantification (BLQ); all rifapentine concentrations at 168 h were BLQ. For isoniazid, 18.2% (157/864) of concentrations were BLQ within 0–48 h, and all measurements obtained from 48–168 h were BLQ. Specifically, in the 0–24-h window, 7.9% (61/768) of all observations were BLQ. All BLQ data points were omitted from the analysis.

The final rifapentine model is a one-compartment model with four transit compartments to account for delayed absorption. Autoinduction, described by an enzyme turnover model, was not statistically significant (− 3.19 ΔOFV) and therefore excluded. The effect of dose on bioavailability, as reported in previously published PK models, shows that increasing the dose of rifapentine reduces its bioavailability [10, 20]. However, this effect was not included in the model since only a single dose level (900 mg) was used in this study. Therefore, the parameter estimates correspond to a 900-mg dose of rifapentine. The final isoniazid model is a two-compartment model with five transit compartments for delayed absorption. A well-stirred liver model was not chosen, as it led to a poorer fit (+ 3.42 ΔOFV) and lacked data on acetyl-isoniazid. Since N-acetyltransferase 2 genotyping information was not available, a mixture model was used to differentiate between fast/intermediate and slow acetylator subpopulations in terms of clearance. The inclusion of allometric scaling did not improve the

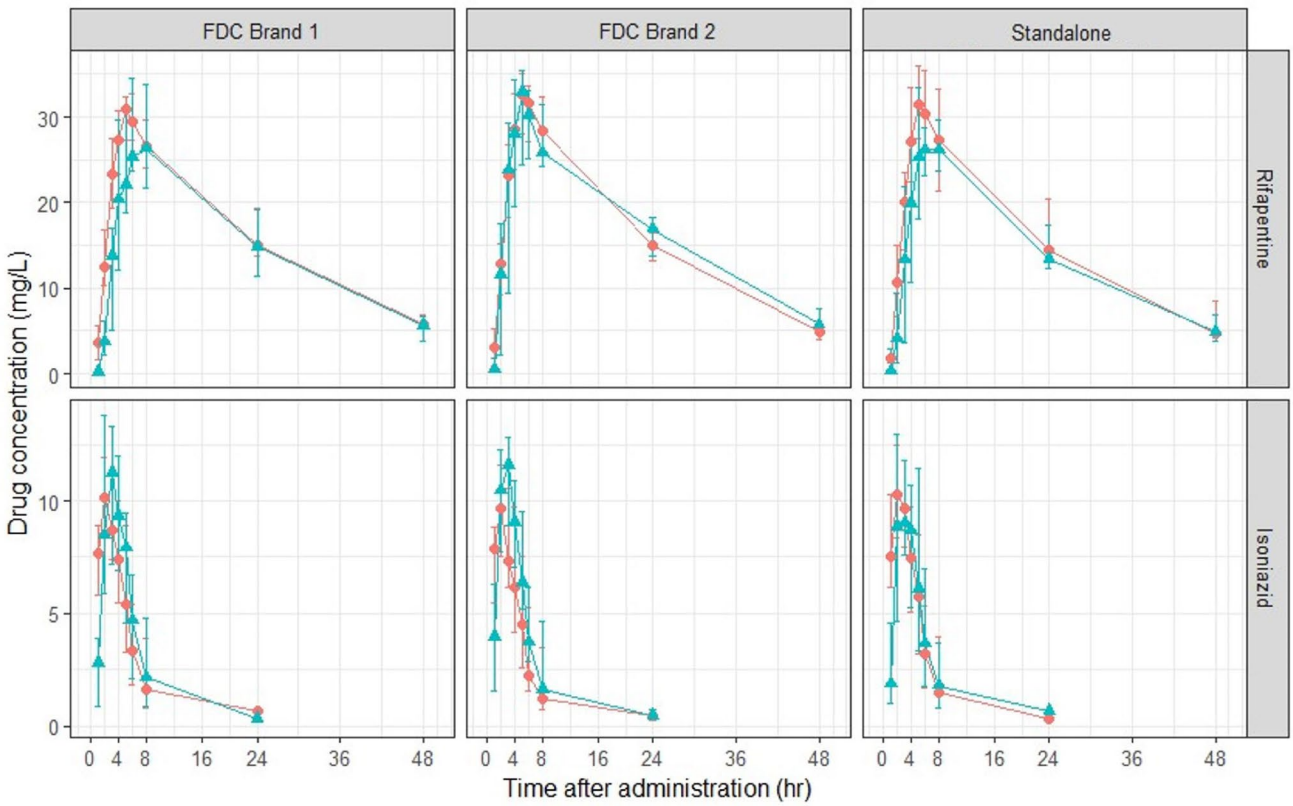

Fig. 2 Observed concentrations of rifapentine and isoniazid. The *green line with triangles* represents the median concentration and 1st and 3rd quantiles for the whole tablet, while the *red line with dots* represents the median concentration and 1st and 3rd quantiles for the suspension. *FDC* fixed-dose combination

model fit for rifapentine when using body weight or fat-free mass. However, it improved the model fit for isoniazid when fat-free mass was used (− 3 ΔOFV). Therefore, allometric scaling with a fat-free mass on CL and V was incorporated into the isoniazid model. Parameter estimates are summarized in Table 2. The NONMEM model code can be found in ESM 2 and 3. The VPCs of the final model for rifapentine and isoniazid, shown in Figs. 3, 4A and B, illustrate the well-predictive performance of the final model.

The relative bioavailability of rifapentine suspended in water was significantly higher than that of the whole tablet reference, with a value of 110.1% (90% CI 100.4–121.0) for FDC brand 1. For FDC brand 2 and the standalone formulation, the relative bioavailability of rifapentine was not significantly different from the whole tablet, with values of 105% (90% CI 95.9–115.5) and 98.9% (90% CI 90.3–108.2), respectively. For isoniazid, the bioavailability of the suspension in water was comparable to that of the whole tablet, with values of 95.2% (90% CI 88.5–102.4) for FDC brand 1 and 102.1% (90% CI 95.0–109.8) for FDC brand 2, but significantly lower for the standalone tablet (89.9%, 90% CI 83.7–96.8). Despite these differences, all generic brands for rifapentine and isoniazid suspended in water showed bioavailability within the bioequivalence criterion range of 80–125%, indicating they were comparable to the whole tablets.

The relative bioavailability of rifapentine and isoniazid in FDC brand 1 and FDC brand 2 whole tablets was estimated to be similar to that of the standalone compound whole tablet, as it falls within the bioequivalence criterion. Detailed results can be found in Supplementary Figure 4 (see ESM). Comparison of relative bioavailability for rifapentine and isoniazid are illustrated in Fig. 5, while comparisons

Table 2 Parameter estimates of the final population pharmacokinetic model for rifapentine and isoniazid

Parameters	Estimates (90% CI)[a]	
	Rifapentine	Isoniazid
Typical parameters		
CL/F (L/h)	1.03 (0.93–1.11)	
Fast/intermediate acetylator (isoniazid) $CL_{Fast/intermediate,isoniazid}$/F (L/h)[b]		23.3 (21.3–25.6)
Slow acetylator (isoniazid) $CL_{Slow,isoniazid}$/F (L/h)[b]		9.5 (8.5–10.6)
Proportion of fast/intermediate acetylator (%)		65.9 (49.9–79.1)
V/F (L)[b]	26.56 (24.98–27.96)	59.6 (55.9–63.2)
MTT (h)	2.34 (2.54–2.97)	1.4 (1.3–1.5)
F	1 (Fixed)	1 (Fixed)
Q/*F* (L/h)[b]		1.26 (1.1–1.5)
Vp/*F* (L)[b]		56.7 (48.4–65.9)
Effect of suspension form on MTT (%)	− 22.2 (− 28.7 to − 15)	− 35 (− 40.3 to − 29.3)
Effect of suspension form on MTT variation (%)	− 45.8 (− 57.1 to − 34.8)	− 62.9 (− 70.8 to − 54.5)
Inter-individual/occasion variability[c]		
IIV on CL (% CV)	19.9 (15.6–26.1)	17.4 (13.6–23.0)
IIV on *F* (%CV)	17.3 (13.5–21.7)	18.1 (14.1–23.1)
IOV on *F* (%CV)	12.2 (10.5–14.5)	7.1 (4.7–9.3)
IOV on MTT (%CV)	39.2 (33.8–45.4)	40.8 (34.9–49.2)
Correlation between IOV on F and MTT	0.37 (0.21–0.45)	
Residual unexplained variability		
Proportional error (%)	8 (7–9.1)	20.8 (19.6–22.1)
Additive error (mg/L)	1.7 (1.6–1.9)	0.11 (0.08–0.13)

CL clearance, *F* bioavailability, *IIV* interindividual variability, *IOV* inter-occasion variability, *MTT* mean transit time, *Q* inter-compartment clearance, *V* volume of distribution, *Vp* volume of distribution of the peripheral compartment

[a]90% confidence interval was obtained using the sampling importance resampling method

[b]An allometric scaling factor is applied to CL, *V*, *Q*, and Vp for isoniazid as: $Pi = P \times \left(\frac{FFM}{45}\right)^{x}$, where P_i is the individual typical parameter; *x* is 0.75 for Cl and *Q* and 1 for *V* and Vp

[c]Variability estimates are reported as the coefficient of variation (%CV), calculated as $\sqrt{e^{\omega^2} - 1} \times 100$

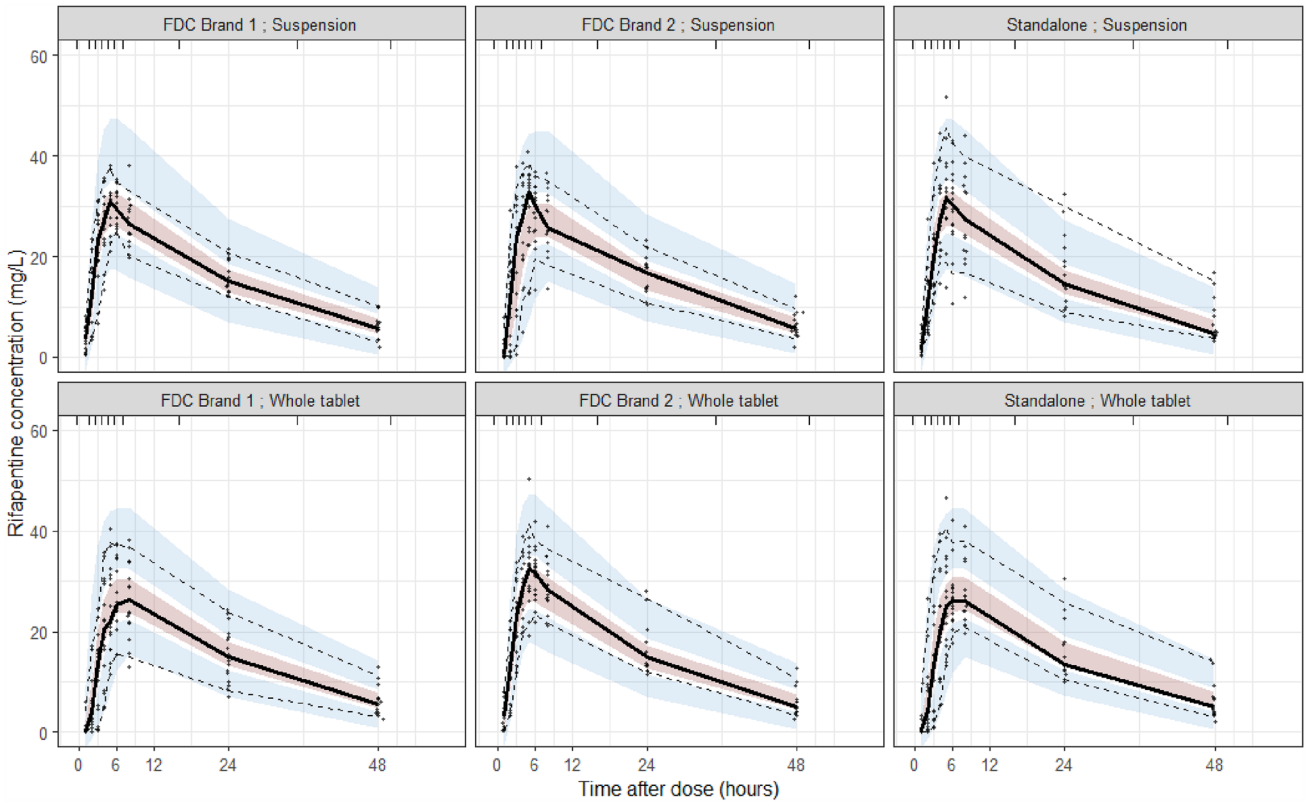

Fig. 3 Visual predictive checks of the final model on observed rifapentine concentrations (*dots*) from time after dosing up to 48 h, stratified by fixed-dose combination (FDC) generic brands or standalone and formulation type (whole tablet or suspension). The *solid black line* represents the 50th percentile of observations, while the *dashed black lines* represent the 5th and 95th percentiles. The *red and blue shaded areas* indicate the 95% confidence intervals of the model predictions

between generic brands of whole tablets are presented in Supplementary Figure 4 (see ESM).

The absorption rate of the suspension was 22.2% (90% CI 12.4–30.8) higher than that of the tablet formulation for rifapentine and 35% for isoniazid (90% CI 26.1–42.6). Furthermore, the inter-occasional variability in absorption rate was lower in the suspension compared with the tablet form, with reductions of 45.8% (90% CI 27.2–59.6) for rifapentine and 62.9% (90% CI 46.6–74.6) for isoniazid.

The secondary PK parameters derived from observed data using NCA analysis are summarized in Table 3. There are no notable differences in the secondary PK parameters between whole tablets and tablets administered as a suspension for either rifapentine or isoniazid. Results from NCA-PPC for both rifapentine and isoniazid, shown in Supplementary Figure 5 (see ESM), indicate that the final models perform well in predicting AUC.

4 Discussion

This study used a population PK modelling approach to compare the relative bioavailability of rifapentine and isoniazid in adults with TB infection after administration of either whole or suspended tablets, in both FDC and standalone forms. Although NCA remains the traditional method for assessing bioavailability, and no specific regulatory guidance yet exists for using population PK in bioavailability or bioequivalence studies, model-informed approaches are increasingly recognized [21, 22]. The population PK approach provides a more robust method, especially for handling inter-occasion variability and for scenarios with pronounced fast- versus slow-acetylator polymorphism that affects isoniazid exposure [11]. To meet regulatory standards, we applied the conventional 90% confidence-interval criterion and confirmed that all formulations fall within the 80–125% bioequivalence margin [14]. The population PK model shows that the bioavailability of whole and suspended tablets is similar based on the bioequivalent criterion for both FDC and standalone formulations. The treatment was generally safe and well tolerated without adverse events related to formulation

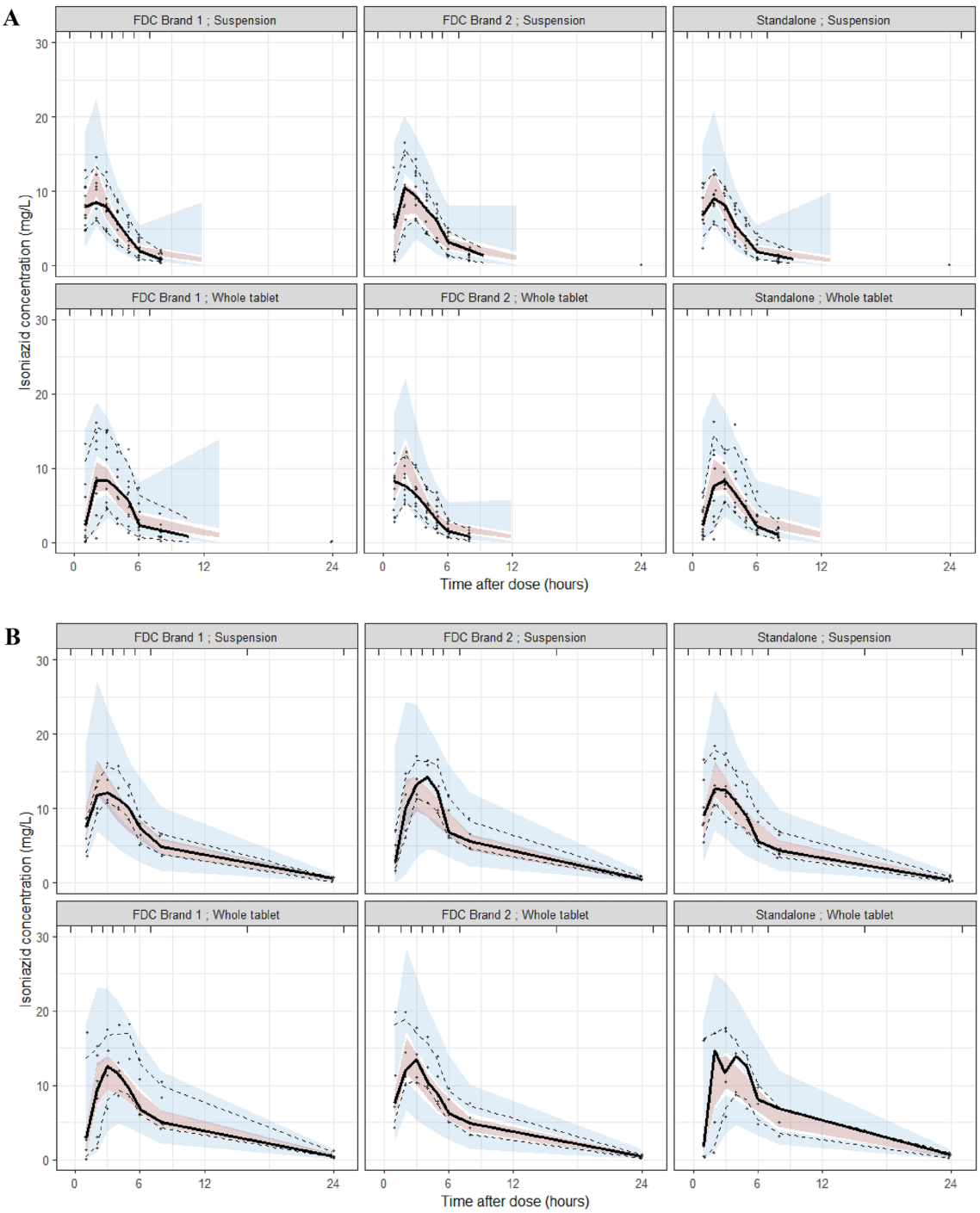

Fig. 4 **A** Visual predictive checks of the final model on observed isoniazid concentrations (*dots*) in the predicted fast/intermediate acetylator population from time after dosing up to 24 h, stratified by fixed-dose combination (FDC) generic brands or standalone and formulation type (whole tablet or suspension). The *solid black line* represents the 50th percentile of observations, while the *dashed black lines* represent the 5th and 95th percentiles. The *red and blue shaded areas* indicate the 95% confidence intervals of the model predictions. **B** Visual predictive checks of the final model on observed isoniazid concentrations (*dots*) in the predicted slow acetylator population from time after dosing up to 24 h, stratified by fixed-dose combination (FDC) generic brands or standalone and formulation type (whole tablet or suspension). The *solid black line* represents the 50th percentile of observations, while the *dashed black lines* represent the 5th and 95th percentiles. The *red and blue shaded areas* indicate the 95% confidence intervals of the model predictions

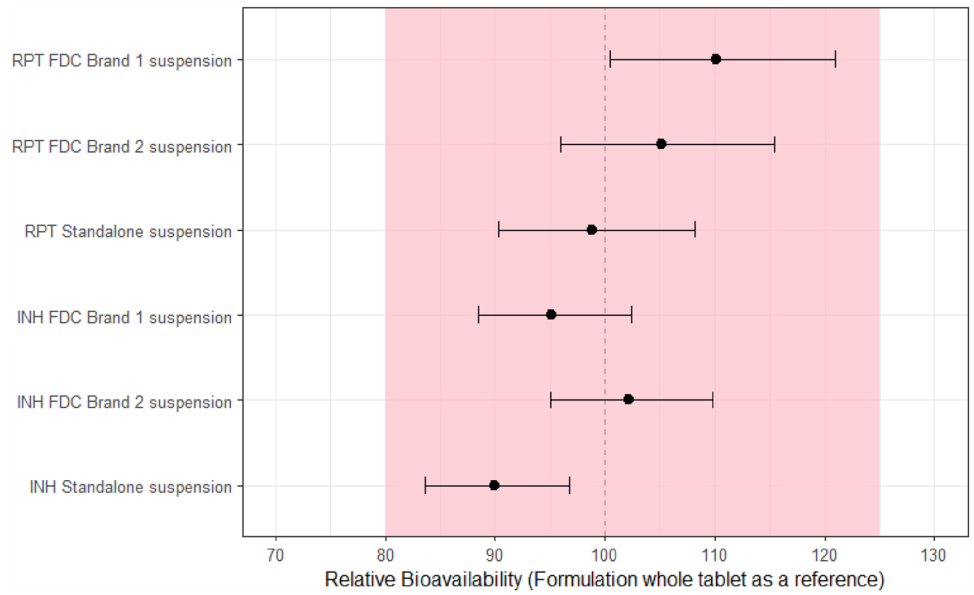

Fig. 5 Estimated relative bioavailability with 90% confidence intervals, obtained via log-likelihood profiling (LLP), using the whole tablet formulation as a reference. The *shaded area* represents the standard bioequivalence range of 80–125%, with a reference line (*dashed*) at 100%. *FDC* fixed-dose combination, *INH* isoniazid, *RPT* rifapentine

Table 3 Secondary pharmacokinetic metrics derived from non-compartmental analysis (NCA)

	$N = 16$	$AUC_{0-168\ h}$ (mg h/L)[a]	C_{max} (mg/L)[a]	T_{max} (h)[a]
Rifapentine				
Suspension	FDC Brand 1	705.9 (584.8, 1008)	31.8 (25.4, 38)	5.49 (4, 8)
	FDC Brand 2	770.9 (442.8, 1019)	34.1 (19.9, 40.8)	5.01 (4, 8)
	Standalone	674 (366.5, 1355)	32.85 (14.7, 51.7)	5 (4, 8)
Whole tablet	FDC Brand 1	675.9 (367.4, 1054)	30.35 (15.7, 40.4)	6 (2.97, 8.1)
	FDC Brand 2	708.5 (592.3, 1177)	34.35 (23.8, 50.3)	5.05 (3, 8)
	Standalone	626.9 (484.6, 1310)	30.15 (22.3, 46.5)	5.5 (4, 8)
Isoniazid				
Suspension	FDC Brand 1	43.18 (19.5, 124.8)	10.8 (6.4, 16.1)	2 (1, 3)
	FDC Brand 2	50.95 (27.2, 136.8)	13.05 (8, 17.1)	2.49 (1.9, 5)
	Standalone	46.59 (17.8, 136.5)	10.75 (5.6, 18.4)	2 (1, 3.)
Whole tablet	FDC Brand 1	56.61 (21.0, 154.5)	13.4 (7.6, 18.2)	2.5 (1.0, 5)
	FDC Brand 2	36.41 (19.4, 142.6)	9.78 (5.2, 19.9)	2 (1, 3)
	Standalone	40.83 (19.0, 139.4)	12.05 (5.55, 17.7)	3 (1.08, 5)

AUC area under the curve, C_{max} maximal concentration, *FDC* fixed-dose combination, T_{max} time to reach maximal concentration

[a]Reported pharmacokinetics metrics are summarized as median (minimum, maximum)

manipulation. The findings suggest that whole tablets can be manipulated into suspension form while maintaining comparable drug exposure.

In this study, the autoinduction of rifapentine was not significant, likely because rifapentine was administered only once a week, which may not have allowed sufficient enzyme induction, and also due to the lack of metabolite measurements. This is consistent with the findings of Weiner et al. [23], and Francis et al. [24], who also observed no autoinduction of rifapentine with a once-weekly dosing schedule. The mixture model for isoniazid estimated the proportion of fast/intermediate acetylators at 65.9% (90% CI 49.9–79.1), in line with another study from the same demographic area [25], but differing from a study in South Africans that reported 47.5% for fast/intermediate acetylator genotypes [26]. This discrepancy may reflect ethnic differences among study participants but could also result from random variation due to the sample size. Additionally, during model development, the model was unable to distinguish between fast and intermediate

acetylator genotypes. This study used a cross-over design without a washout period; however, the dosing interval was sufficiently long to prevent carry-over effects, and the longitudinal modelling approach was designed to account for them. Although secondary PK metrics from NCA were not corrected for carry-over, no significant carry-over effect was observed. Rifapentine has a half-life of approximately 13–17 h, [27] with all rifapentine measurements being BLQ at 168 h, while the half-life of isoniazid is approximately 1–3 h [28], with all isoniazid measurements being BLQ at 48 h. This supports that rifapentine and isoniazid were fully excreted before the next dosing schedule.

The absorption rate of the suspension was higher than that of the whole tablet, with lower variability in absorption rate for both rifapentine and isoniazid. However, this higher absorption rate does not appear to be associated with C_{max}, as it remained similar across formulations, resulting in comparable drug exposure.

Previous studies have indicated a substantial decrease in the AUC for isoniazid when using crushed tablets, with a reduction of 42% (90% CI 23–53 $AUC_{0–10\ h}$) in adult MDR-TB patients and 20% (95% CI 3.7–45.3) reduction in $AUC_{0–24\ h}$ in paediatric patients with latent tuberculosis infection [LTBI] [29, 30]. In the paediatric subgroup of the PREVENT-TB study, the bioavailability of rifapentine was decreased in patients receiving crushed tablets compared with whole tablets, with a 1.3-fold higher geometric mean $AUC_{0–inf}$ of rifapentine in those receiving whole tablets, in line with another recent study in paediatric patients with LTBI [23, 30]. The differences could potentially be explained by the more standardized approach to formulation manipulation in our study. However, in real-world settings, drug exposure may be reduced due to factors such as incomplete ingestion of the full dose and residual drug loss during tablet manipulation. In addition, our study had a higher proportion of female participants. However, given the cross-over study design, we do not expect this to have significantly influenced our findings. The lack of improvement when using fat-free mass instead of total body weight in the allometric scaling may be explained by the narrow body weight range (51–66 kg) and high proportion of females in our cohort (83%).

The findings of this study can be directly applied to bridging rifapentine and isoniazid dosing for paediatric use, as no dose adjustment is required when the tablets are suspended. Previous population PK models have shown that increased doses may reduce bioavailability due to saturable absorption [10, 20]. However, the dose-effect on bioavailability may not be clinically relevant, as it has been reported to result in only a 1.7% to 2.5% reduction in bioavailability for each 100-mg increase above 300 mg of rifapentine.

This study has a significant impact on clinical practice and has the potential to increase access to the preventive treatment 3HP regimen, where the dispersible formulation of rifapentine is not available. Notably, the latest WHO guidelines now include rifapentine dosing recommendations for children as young as 3 months [5].

5 Conclusions

Rifapentine and isoniazid, as both FDC and standalone tablets, achieved similar bioavailability when administered as whole tablets or when suspended in water. Therefore, suspending these formulations in water allows for rifapentine/isoniazid dosing in young children and others who cannot readily swallow whole tablets without requiring rifapentine or isoniazid dose adjustment. While access to paediatric rifapentine formulations is still very limited in the field, these findings will help improve access to the 3HP regimen and potentially other rifapentine-containing regimens in children in real-world settings.

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Declarations

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Competing Interests Elin M. Svensson is an Editorial Board member of Clinical Pharmacokinetics but was not involved in the selection of peer reviewers or in any subsequent editorial decisions related to this manuscript. The other authors declare no competing interests.

Ethical Approval The study was approved by the Stellenbosch University Health Research Ethics Committee (reference number 26169), the South African Health Products Regulatory Authority (Trial Reference 20220905) and the WHO Ethical Review Committee (Reference ERC.0003837) prior to initiation. The trial is registered with the Pan African Clinical Trials Registry (PACTR202306775627089).

Consent to Participate All adults provided written informed consent in the home language of their choice prior to their inclusion in the studies. No personally identifiable information is presented in this article.

Consent for Publication All participants provided consent for publication

Availability of Data and Materials Data will be made available upon reasonable request to the corresponding author.

Code Availability The code used for the final model is provided in ESM S2 for the rifapentine model and in ESM S3 for the isoniazid model.

Authors' Contributions S. Janssens coordinated the study, contributed to the study design, and drafted the manuscript. T. Vongjarudech was responsible for conducting the modelling and analysis and contributed to drafting the manuscript. A.C. Hessling and E.M. Svensson contributed to the study design and analysis and provided supervision. All authors have approved the final manuscript.

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