Population Pharmacokinetics and Exposure–Response Analysis of a Fixed-Dose Combination of Ivermectin and Albendazole in Children, Adolescents, and Adults

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Trichuris trichiura **is a soil-transmitted helminth causing intestinal disease. Albendazole is the standard treatment despite its moderate efficacy, which is improved when co-administered with ivermectin. A fixed-dose combination adds practical advantages mainly for mass drug administration. The aim of this article is to define the population pharmacokinetic models and exposure–response of an innovative albendazole/ivermectin combination. Data were obtained from a phase I clinical trial in healthy adults and from a phase II trial in children and adolescents infected with *T. trichiura*. Nonlinear mixed-effects models were built for albendazole and ivermectin using NONMEM®. Area under the curve was calculated using the empirical Bayes estimates of the pharmacokinetic parameters of each individual and used for evaluation of exposure–response between cure rate and pharmacokinetic exposure. The pharmacokinetics of albendazole was described using a two-compartmental model with first-order absorption and the pharmacokinetics of ivermectin was described using a two-compartmental model with zero-order followed by first-order absorption. Clearance and volume of distribution increased with body weight for both albendazole and ivermectin. Day 1 area under the curve of albendazole and ivermectin from the children and adolescents treated with the combination regimens were similar to the healthy adults treated with control drugs. A flat exposure–response relationship was observed between the cure rate and drug exposure. Population pharmacokinetic of a combination of albendazole and ivermectin in children, adolescents, and adults, either healthy or infected by *T. trichiura* was described. The dosage selected in the phase II trial was appropriate for the subsequent phase III.**

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ There is only published one pharmacokinetic study after single-dose administration in adults of the ivermectin/albendazole fixed-dose combination. There is no information on children or patients, nor a population pharmacokinetic model.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ What is the difference between the PK of albendazole and ivermectin in the FDC orodispersible tablet and the regular Eskazole® and Stromectol® tablets? How demographic covariates, such as weight, age, sex and race, and disease status impact the PK? Did the FDC regimens selected for the phase III trial achieve target albendazole and ivermectin exposure?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This study characterized the population pharmacokinetics of both albendazole and ivermectin of the FDC formulation in children, adolescents, and adults. The models were used to confirm the exposure and efficacy of the selected dose regimens for the phase III trial in children and adolescents.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The albendazole and ivermectin population PK models reported in this study could be useful for future development of albendazole and ivermectin combinations against STH. The results confirm that the FDC dose regimens selected to continue with the clinical program were adequate. Moreover, this study was a requirement of the Health Authority, for the authorization of the new drug, a mandatory step to allow the access of the medicine to the patient.

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Soil-transmitted helminths (STH) refer to a group of intestinal worm species transmitted through contaminated soil, including *Trichuris trichiura*. STH infections are usually mild, but heavy infections can cause abdominal pain, diarrhea, anemia, protein loss, rectal prolapse, and other health conditions. The infection often compromises growth and development in children.

STH are the most prevalent of all neglected tropical diseases worldwide and disproportionately affect impoverished populations, causing significant morbidity in children.[1,2]

Besides hygiene measures, the core intervention for reducing STH morbidity is preventive chemotherapy through periodic mass drug administration (MDA) campaigns,[3] which is achieved by large-scale distribution of anthelmintic drugs, to at-risk population in high-prevalence areas.

Albendazole is a standard treatment against STH, with proven safety and variable efficacy across the different species of STH. Albendazole exhibits larvicidal, ovicidal, and vermicidal activity and exerts intra-luminal anthelmintic action. Albendazole is poorly absorbed (< 5%) and undergoes extensive first-pass metabolism to its primary metabolite, albendazole sulfoxide. Its efficacy against *T. trichiura* is poor,[4] estimated to be 31%, and seems to have decreased to 15% in the last years.[4]

Given this situation, there is an increasing need to identify new therapeutic regimens with improved efficacy while maintaining or improving safety to support the current WHO strategy to interrupt STH transmission.[5,6]

Ivermectin, a derivative of the avermectins, is a mixture containing > 90% of 5-O-demethyl-22,23-dihydroavermectin A1a ($H2B_{1a}$) and < 10% of 5-Odemethyl-25-de(1-methylpropyl)-22 ,23-dihydro-25-(1-methylethyl) avermectin A1b ($H2B_{1b}$). Once absorbed, ivermectin is metabolized in the liver and excreted almost exclusively in the feces. Ivermectin is highly effective, used in animals and humans against several diseases in addition to STH, including onchocerciasis, lymphatic filariasis, strongyloidiasis, and scabies. Considering its broad spectrum, ivermectin is an attractive option for combination or co-administration with albendazole in settings where multiparasitism is the norm.[7]

Both ivermectin and albendazole are included on the WHO's list of essential medicines for the treatment of STH.[8,9] Co-administration therapy with existing drugs against STH has been identified as a useful strategy potentially more effective than monotherapy. Particularly, co-administration of albendazole and ivermectin has several proven advantages, such as improved efficacy against *T. trichiura*[10–12] and decreased risk of drug resistance due to the two different mechanisms of action.[13]

The use of a fixed-dose combination (FDC) compared with the co-administration of separate tablets adds practical advantages in storage, transportation, and handling, easier dispensation by healthcare professionals, and higher acceptability by patients. Therefore, it is preferred by non-medical personnel[3] for facilitating large-scale MDA and community-based treatments, who are the key to successfully controlling STH in high-prevalence areas.[14] In a large-scale campaign, the need to weigh the patient to adjust a dose is considered "labor- and time-intensive," and hence, a constraint.[15] The development of an FDC of albendazole/ivermectin for adults (400/18 mg) and children below 45 kg (400/9 mg strength) was part of public–private partnership aiming to treat and prevent poverty-related infectious diseases.

The clinical program for the development of the FDC included a phase I bioavailability study in healthy adults,[16] followed by an adaptive phase II/III safety and efficacy clinical trial.[17] The phase II was a dose-finding study in children infected with *T. trichiura* that embedded a pharmacokinetic sub-study hereby included. Complete study population description, safety, and efficacy results from this study are published elsewhere.[18]

The aim of the present manuscript is to define the population pharmacokinetic (PPK) models developed with the data obtained from the phase I and the phase II trials conducted under the clinical development program for the FDC. Exposure–response relationship (E–R) was also evaluated to confirm the dose regimens selected to conduct the phase III clinical trial in children and adolescents with STH infection.

MATERIALS AND METHODS

Study design and ethics

The analysis data were obtained from two clinical trials: (1) A phase I, human pharmacology, single-dose, open-label, laboratory-blinded, sequence-randomized, three-treatment, three-period crossover study in healthy adults comparing bioavailability of the FDC to each of the active substances; (2) A phase II, randomized, controlled, parallel-group, open-label, assessor-blinded, dose escalation and pharmacokinetics trial in children or adolescents with trichuriasis (ClinicalTrials.gov ID: NCT05124691).

Both trials were reviewed by the corresponding Ethics Committees and authorized by the Health Authorities of Portugal (phase I) and Kenya (phase II). The studies were conducted in accordance with the Declaration of Helsinki and with Good Clinical Practices and in compliance with European Medicines Agency (EMA) guidelines and applicable local laws. Written consent was obtained from parents and written assent for participants 12–17 years old.

Treatments

In the phase I study, adult volunteers received in three different periods a single dose of albendazole/ivermectin 400/18 mg FDC tablet (Liconsa, SA), albendazole 400 mg (Eskazole®, Smith-Kline&French Laboratories) and six tablets of ivermectin 3 mg (Stromectol®, Merck, Sharp & Dohme BV).

Phase II evaluated three treatment arms: (1) One single dose of FDC; (2) One FDC tablet per day for 3 days; (3) One single tablet of albendazole 400 mg. All treatments administered together with a light meal consisting of 200 mL whole milk and five regular biscuits. Since phase II trial was a dose-escalation study with the main objective of demonstrating the safety of FDC, participants were sequentially assigned to three consecutive groups receiving increasing adjusted doses per kg body weight of

Table 1 Dose escalation by weight range in the phase II study

Group	Weight range	Treatment arm	Ivermectin adjusted dose
Group 1 ($n=38$)	23.0–29.9 kg	FDC 9/400 mg × 1 day	300–391 µg/kg × 1 day
		FDC 9/400 mg × 3 days	300–391 µg/kg × 3 days
		ALB 400 mg × 1 day	N.A.
Group 2 ($n=38$)	30.0–44.9 kg	FDC 18/400 mg × 1 day	400–600 µg/kg × 1 day
		FDC 18/400 mg × 3 days	400–600 µg/kg × 3 days
		ALB 400 mg × 1 day	N.A.
Group 3 ($n=50$)	15.0–22.9 kg	FDC 9/400 mg × 1 day	391–600 µg/kg × 1 day
		FDC 9/400 mg × 3 days	391–600 µg/kg × 3 days
		ALB 400 mg × 1 day	N.A.

ivermectin (**Table 1**). The progression along groups was authorized by a Data Safety Monitoring Board after meticulous evaluation of the benefit/risk profile.

Pharmacokinetic evaluation

Intensive PK samples were collected in the healthy subjects in the phase I trial, with 21 venous blood samples obtained from pre-dose to 72 hours post-dose in each of the study period.

Sparse samples were collected by finger prick using Mitra Clamshell Devices® in the infected children and adolescents in the phase II trial.

Blood sampling covers the following timepoints: (a) IVM/ALB × 1 day: 1, 2, 3, 4, 5, 6, 7, 8, 24, 48 and 72 hours after treatment administration. (b) IVM/ALB × 3 days: 48 hours (pre-dose 3), 49, 50, 51, 52, 53, 54, 55, 72, 96 hours and 120 hours post-first administration in day 0. (c) ALB: 1, 2, 3, 4, 5, 6, 7, 8 and 24 hours after treatment administration. The sampling times were organized in groups of two timepoints (for the arms with only 1-day treatment) or three timepoints (for the arm with 3 days of treatment). When a participant entered the trial, he/she was randomly assigned to a treatment arm and a sampling time group (for detailed information, please refer to **Supplementary Material**).

Samples were maintained at −80°C until shipment to the bioanalytical laboratory (Kymos Pharma Services SL, Barcelona, Spain). Bioanalysis was validated and carried out in accordance with the applicable international guidelines (CEDER Industry and EMA guidance on Validation of Bioanalytical Methods).

Albendazole sulfoxide concentration in plasma was determined using a liquid chromatography with tandem mass spectrometry (LC–MS/MS) validated method with a lower limit of quantification (LLOQ) of 1 ng/mL. Ivermectin-$H2B_{1a}$ concentration in plasma samples were analyzed using a validated LC–MS/MS method with a LLOQ of 1 ng/mL in phase I and 5 ng/mL in phase II. This difference is because in phase I the method for $H2B_{1a}$ was based on 100 µL of plasma, but in phase II, the LLOQ for the whole blood assay was compromised by the low dry whole blood volume (20 µL) of sample collected in a Mitra microsampling device. Samples that were below LLOQ limit were replaced with zero and flagged as such. Samples with missing concentration or missing sampling time were excluded. Samples with high conditional weighted residuals ($|CWRES| \geq 6$) were excluded.

Pharmacokinetic modeling

A PPK model of albendazole sulfoxide and a PPK model of ivermectin $H2B_{1a}$ were developed according to the corresponding EMA Guideline[19] and as previously described.[20,21] The pharmacokinetic modeling software used was NONMEM (Version 7.5.0 m ICON).

A one- and two-compartment models were tested for both albendazole sulfoxide and ivermectin $H2B_{1a}$. Absorption was modeled as a first-order process for albendazole, and zero-order release followed by a first-order process for ivermectin.

For the two-compartment models, the following PK parameters were estimated: clearance of the central compartment (CL/F), volume of distribution of the central compartment (V/F), inter-compartment clearance (Q/F), and volume of distribution of the peripheral compartment (Vp/F). For the first-order absorption, relative bioavailability (F1), the first-order absorption rate constant (Ka), and absorption lag time (t_{lag}) were estimated. Additionally, the duration of the zero-order release (D1) was estimated for zero-order release followed by first-order absorption.

Impact of demographic covariates on the PK, including age, body weight (WT), body mass index (BMI), sex and race (European vs. African), and disease status (healthy vs. infected) were evaluated using a univariate screening followed by a backward elimination process. Significant covariates identified ($P < 0.01$ in likelihood ratio test) in the univariate screening were added to the structural model to form a full model. During the backward elimination process, covariates were removed from the model one at a time if their deletion led to insignificant model deterioration ($P > 0.001$). If covariates show a correlation of > 0.7, only one of the correlated covariates was considered to be included in the formal analysis. This was either the covariate with the strongest influence as determined by exploratory graphical analysis or the variable that is most meaningful from a clinical, biological, or practical perspective.

Model diagnostics were performed using residual-based goodness-of-fit plots. The predictability of the PK model was evaluated using prediction-corrected visual predictive check (pcVPC) with 500 replicates in the simulations.

Exposure–response of efficacy

Exploratory analysis of exposure–response (E–R) between efficacy and PK exposures was conducted using the results in the phase II trial. The efficacy end point explored as cure rate (CR) for *T. trichiura*, defined as the absence of eggs in the stool, was determined by Kato-Katz test 21 days after treatment.

Albendazole sulfoxide and ivermectin $H2B_{1a}$ concentrations area under the curve (AUC) were calculated using empirical Bayes estimates of the final PK models and used as PK predictors. AUC was calculated by the linear-up/log-down trapezoidal rule (phase I study) and using the *post hoc* PK parameters of the PPK model. Guided by exploratory plots, the potential E–R relationship was described using a linear logistic regression model. The AUC of albendazole sulfoxide and ivermectin $H2B_{1a}$ were also compared between the healthy adult subjects in the phase I trial and infected children and adolescents in the phase II trials to ensure comparable exposures were achieved in the phase II.

RESULTS

Participants

The PPK analyses included 75 healthy adults (phase I) and 123 infected children and adolescents (phase II). None of the subjects

Table 2 Covariates included in the model per treatment received

Study	Phase I (*N* = 75)	Phase II (*N* = 123)
Age (year)		
Median [Min, Max]	30.0 [19.0, 59.0]	9.00 [5.00, 17.0]
Weight (kg)		
Median [Min, Max]	71.0 [54.2, 95.7]	25.2 [15.1, 45.0]
Height (cm)		
Median [Min, Max]	172 [154, 190]	129[105, 162]
BMI (kg/m^2)		
Median [Min, Max]	24.5 [19.1, 29.9]	14.0 [12.0, 21.0]
Sex		
Female	33 (44.0%)	52 (42.3%)
Male	42 (56.0%)	71 (57.7%)
Race		
Black or African American	6 (8.0%)	123 (100%)
White or European	62 (82.7%)	0 (0%)
Other	7 (9.3%)	0 (0%)

BMI, body mass index.

were completely excluded. The model for albendazole sulfoxide included 3,025 samples from 198 subjects, and the model for ivermectin $H2B_{1a}$ included 2,894 samples from 174 subjects (complete data are provided in **Table S1**).

Summary of the demographic and baseline covariates by treatment is provided in **Table 2**.

Population PK model for albendazole sulfoxide

Albendazole sulfoxide PK was described using a two-compartment model with first-order absorption into the central compartment and linear elimination from the central compartment. The model structure is provided in **Figure 1a**.

Final PPK parameter estimates are presented in **Table 3**. For a typical male adult subject weight 70 kg, CL/F of albendazole sulfoxide was estimated to be 82.3 (3.66% RSE) L/hour, Vc/F was 845 (6.79% RSE) L, Q/F was 46.4 (4.64% RSE) L/hour and Vp/F was 508 (13% RSE) L. The typical elimination half-life was estimated to be 15.5 hr. Bioavailability of albendazole in the FDC formulation was 78.5% of the Eskazole®.

Body weight and sex were the only significant covariates on the albendazole sulfoxide PK. The final PK parameter and covariate relationship are given as:

$$CL/F_i = 82.3 \times \left(\frac{WT_i}{70}\right)^{0.302} \times (1 - 0.102\ (\text{if female}))$$

$$Vc/F_i = 845 \times \left(\frac{WT_i}{70}\right)^{0.915}$$

$$Q/F_i = 46.4 \times \left(\frac{WT_i}{70}\right)^{0.302}$$

$$Vp/F_i = 508 \times \left(\frac{WT_i}{70}\right)^{0.915}$$

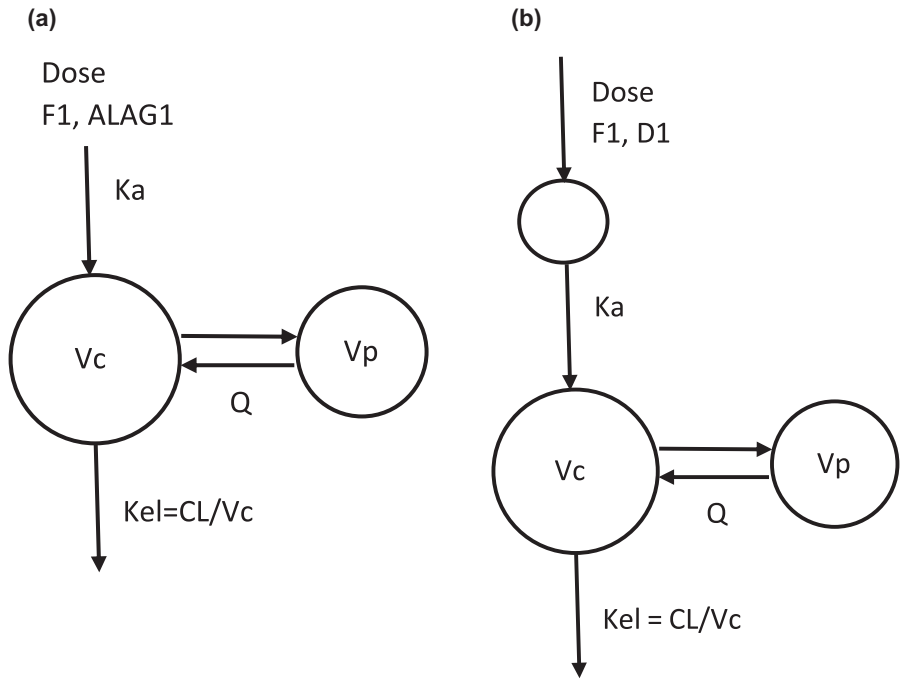

Figure 1 Population pharmacokinetic model structure for albendazole (**a**) and ivermectin (**b**).

Table 3 Population parameter estimates for the final albendazole PPK model

Parameter	Unit	Estimate	RSE (%)	Shrinkage (%)
CL/F	L/hour	82.3	3.66	
Vc/F	L	845	6.79	
Q/F	L/hour	46.4	4.64	
Vp/F	L	508	13	
Ka	1/hour	1.34	6.14	
Tlag	hours	0.941	0.103	
F1_Combo		0.785	0.468	
WT on CL/F and Q/F		0.302	18.2	
WT on Vc/F and Vp/F		0.915	10.1	
SEXF on CL/F		−0.102	40.2	
IIV or IOV				
ω^2_CL/F		0.125	15.1	15.1
ω_Vc/F×ω_CL/F		0.139	16.8	
ω^2_Vc/F		0.230	13.5	17.9
ω^2_Vp/F×ω_CL/F		0.173	24.2	
ω^2_Vp/F×ω_Vc/F		0.269	22.3	
ω^2_Vp/F		0.612	21.1	26.2
ω^2_Ka		0.853	21.7	26.9
ω^2_Ka (IOV)		1.58	16.9	48.3
Residual error				
δ^2 (Log-Additive)	%	0.0686	1.17	8.5

IIV was reported as variance (ω^2); RSE calculated as standard error/estimate×100 (%).
BSV, between-subject variability; CL/F, apparent clearance; F, oral bioavailability; IIV, interindividual variability; IOV, inter-occasion variability; Ka, first-order absorption rate; PPK, population pharmacokinetics; Q/F, apparent intercompartmental clearance; RSE, relative standard error; Vc/F, apparent volume of the central compartment; Vp/F, apparent volume of the peripheral compartment; WT, body weight.

where subscript *i* represents participant *i*th and WT = body weight.

Other covariates evaluated, including age, race, and disease (healthy vs. STH infected), had no impact on the PK after accounting for the difference in body weight.

The pcVPC suggests the model well describes the albendazole sulfoxide PK for both FDC and Eskazole® (**Figure 2**). Additional model diagnostic plots and NONMEM script are available in Sections 3, 4, and 5 of **Supplemental Material**.

PPK model for ivermectin

Ivermectin PK was described using a two-compartment model with linear elimination from the central compartment. Absorption of ivermectin was modeled as zero-order release followed by a first-order absorption into the central compartment. Model structure is provided in **Figure 1b**.

The final PPK model parameter estimates are presented in **Table 4**. For a typical male adult subject weight 70 kg, CL/F was estimated to be 16.4 (4.41% RSE) L/hour, Vc/F was 48.1 (13.8% RSE) L, Q/F was 23.3 (3.76% RSE) L/hour and Vp/F was 588 (5.39% RSE) L. The typical elimination half-life was estimated to be 43.6 hour. Bioavailability of ivermectin in the FDC formulation was 116% of Stromectol®.

Body weight was the only significant covariate on the ivermectin PK. The final PK parameter and covariate relationship are given as:

$$CL/F_i = 16.4 \times \left(\frac{WT_i}{70}\right)^{0.444}$$

$$Vc/F_i = 48.1 \times \left(\frac{WT_i}{70}\right)^{0.725}$$

$$Q/F_i = 23.3 \times \left(\frac{WT_i}{70}\right)^{0.444}$$

$$Vp/F_i = 588 \times \left(\frac{WT_i}{70}\right)^{0.725}$$

where subscript *i* represents participant *i*th, WT = body weight.

After including body weight on volume and clearance, the impact of age, sex, race and disease status (healthy vs. STH infected) were not significant on the ivermectin PK. The pcVPC curves are shown as **Figure 3**, suggesting the model describes the ivermectin PK in both FDC and the Phase I and Phase II trials well. Additional model diagnostic plots and NONEM script are available in Sections 3, 6, and 7 of **Supplemental Material**.

Pharmacokinetic exposure in phase II

The design of the FDC dose regimens in the phase II trial was to allow for the children and adolescents to achieve similar albendazole and ivermectin exposure compared with the adult subjects in the phase I trial. Day 1 albendazole and ivermectin AUC were calculated using empirical Bayes estimates of the PK parameters from the PK models and the actual dose administrated. The results are summarized in **Table 5**.

Day 1 AUC of albendazole sulfoxide and ivermectin $H2B_{1a}$ were similar between healthy adults treated with control monotherapy in the phase I study and infected children and adolescents treated with FDC in the phase II trial. The AUC on day 1 of the infected children or adolescents treated with FDC in the phase II trial was similar to the AUC in healthy adults treated with Eskazole® 400 mg tablets in the phase I trial. Similarly, the Day 1 ivermectin AUC in pediatric or adolescents in the phase II trial was comparable to the AUC in the adult subjects treated with Stromectol® 6 × 3 mg tablets in the phase I trial. Off note, total AUC of the subjects treated with the FDC × 3 regimen in the phase II trial was threefold greater than that of the day 1 AUC values.

Exposure–response analysis

In the phase II trial, CR for *T. trichiura* was 29.2% in children and adolescents treated with albendazole 400 mg alone, that increased to 75.5% in subjects treated with a single dose of FDC. In subjects

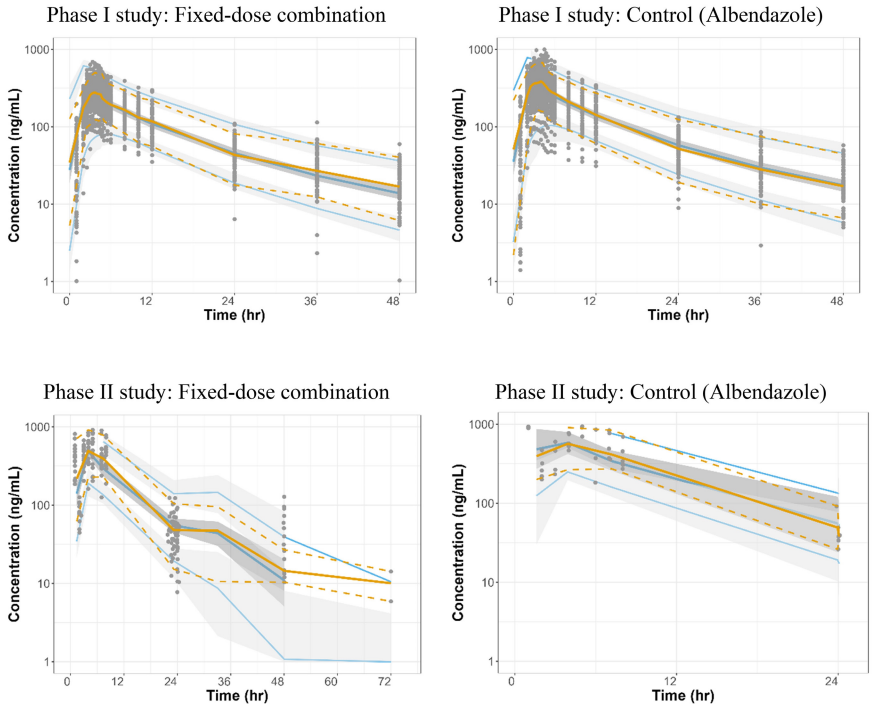

Figure 2 pcVPC for final albendazole sulfoxide PPK model for Phase I and Phase II studies, after the administration of either fixed-combination albendazole/ivermectin or corresponding albendazole control. Gray dots are prediction-corrected observed concentrations. Orange dashed lines are the 95th, 50th, and 5th percentiles of the observed data. Blue lines are the 95th, 50th and 5th percentiles of the simulations. The gray shaded region indicates the 5th to 95th percentile prediction interval.

treated with three doses of FDC the CR reached 98%. Although the phase II population included only 10% of the total of the adaptative phase II/III study, the efficacy results are consistent with phase III results.[18]

The E–R relationship between CR and PK exposure in each treatment group was further explored. As illustrated in **Figure 4**, no E–R relationship between CR and day 1 AUC of albendazole was observed within the treatment group, where the slope of the linear logistic regression model was not significant ($P > 0.05$). Similarly, no E–R relationship between CR and day 1 AUC of ivermectin was observed within each cohort in phase II (**Figure 5**). The flat E–R relationship between CR and ivermectin and albendazole within each treatment group suggests that the current Phase II/III FDC × 1 or FDC × 3 dose regimens achieved appropriate drug exposure in the children and adolescents infected with STH.The FDC regimens were safe in adults, children, and adolescents, and no severe adverse events were reported in any of the included trials.

DISCUSSION

The STOP consortium was created to develop and supply a new medicine to treat STH to developing countries to be evaluated by EMA through the regulatory pathway called *Medicines for All (M4all)*. With this procedure, EMA aims to facilitate access to essential medicines in low- and middle-income endemic countries, including new or improved therapies for unmet medical needs, to prevent or treat diseases of major public health interest. The benefit is to obtain a rigorous scientific assessment by EMA to facilitate the registration in target countries.[22]

In 2018, EMA reviewed the clinical program, suggested guidelines[23,24] and included a phase I bioavailability study in healthy adults and a phase II/III adaptative trial in infected children and adolescents. This PPK analysis was also required by the Health Authority. This publication describes the PPK analysis of albendazole sulfoxide and ivermectin $H2B_{1a}$ in healthy adults (phase I trial) and children and adolescents with trichuriasis (phase II trial). The analysis included 5,919 plasma samples involving 198 participants. From the bioanalytical perspective, this study has limitation due to the aim to reduce as much as possible the sampling to the infected children, only the main analytes were quantified in those samples (albendazole sulfoxide and $H2B_{1a}$) whereas in the healthy adults also the secondary analytes were measured (the parent compound albendazole and the isoform $H2B_{1b}$). Another bioanalytical weakness was that in children the LLOQ of ivermectin increased from 1 to 5 ng/mL, due to the small volume of samples obtained in children (only 20 µL blood per sample) that did not allow the limit obtained for adults.

The PK of albendazole was described by a two-compartment model with first-order absorption and linear elimination, and ivermectin was described by a two-compartmental model with zero-order followed by first-order absorption. The PPK models well described the PK results in both trials, with a relatively high precision in the estimation of the key model parameters (RSE < 7% in the case of albendazole and RSE < 14% in the case of ivermectin). To note, in the case of ivermectin, some very high CWRES for high concentrations were observed, that can be attributed to some samples at the early absorption phase with CWRES between −5 and −8, which is expected since the model did not include variability on Tlag. A

Table 4 Population parameter estimates for the final ivermectin PPK model

Parameter	Unit	Estimate	RSE (%)	Shrinkage (%)
CL/F	L/hour	16.4	4.41	
Vc/F	L	48.1	13.8	
Q/F	L/hour	23.3	3.76	
Vp/F	L	588	5.39	
Ka	1/hour	0.218	8.13	
D1	hours	0.9	12.3	
Tlag	hours	0.739	1.52	
F1 for FDC		1.16	1.27	
Ka for FDC		0.216	9.76	
D1 for FDC		1.37	14.7	
Tlag for FDC		0.701	1.25	
WT on Vc/F and Vp/F		0.725	11.6	
WT on CL/F and Q/F		0.444	11	
IIV or IOV				
ω^2_CL/F		0.107	12.7	15.4
ω_CL/F×ω_Vc/F		0.0444	83.9	
ω^2_Vc/F		0.279	36.5	40.8
ω^2_Ka		0.0405	37	45.5
ω^2_D1		1.05	25	33.7
ω^2_IOV_D1		1.25	14.6	52.5
Residual error				
δ^2 (Log-Additive)		0.0799	1.17	7.3

IIV was reported as variance (ω^2); RSE calculated as standard error/estimate×100 (%).
BSV, between-subject variability; CL/F, apparent clearance; D1, duration of zero-order drug release; F, oral bioavailability; IIV, interindividual variability; IOV, inter-occasion variability; Ka, first-order absorption rate; PPK, population pharmacokinetics; Q/F, apparent intercompartmental clearance; RSE, relative standard error; Vc/F, apparent volume of the central compartment; Vp/F, apparent volume of the peripheral compartment.

more complex absorption model was not tested since the current well describes the peak of the ivermectin PK profile (**Figure 3**).

One of the complexities of these PPK analyses was to handle the confounded covariates in the model development. Subjects enrolled in the phase I trial were healthy adults, who were mostly white, while subjects enrolled in phase II trial were infected children or adolescents who were all African. Sample collection methods were also different where serial venous blood samples were collected in the phase I trial while sparse PK samples were collected in the phase II by finger prick. Considering the correlation between covariates, body weight on clearance and volume were included in the model before evaluating other correlated covariates, including age, height, BMI, and disease status. In the albendazole PPK model, the coefficients of weight were estimated to be 0.302 and 0.915 for clearance and volume, respectively. Compared with male subjects of the same weight, females were 10% lower in the clearance of albendazole. In the ivermectin PPK model, the coefficients of weight were estimated to be 0.444 and 0.725 for clearance and volume, respectively. No additional covariate was identified in the PPK models of albendazole and ivermectin after including the effect of weight.

Hofmann *et al.*[25] recently described the PK characterization of albendazole (given alone) in a similar population of patients aged 2–65 years infected with *T. trichiura* using the same method of finger prick sample extraction (Mitra Clamshell Devices®). The model also describes a two-compartments distribution for albendazole sulfoxide, assuming a first-order absorption and linear elimination. On the covariate analysis, they also agreed that inclusion of body weight on clearance parameters and volume of distribution significantly improved the model fit, although the coefficient was fixed to the typical values of 0.75 and 1 for clearance and volume, respectively. The estimation of albendazole sulfoxide PK parameters by Hofman *et al.* were 1.7 L/h for clearance and 64.3 L for central volume. Considering the 5% bioavailability reported, the values (CL/F = 34 L/h; VcF = 1,286 L) are considered to be similar to the values estimated in current analysis (CL/F = 82.3 L; Vc/F = 845 L).

Ivermectin was also studied by Duthaler *et al.*,[26] who conducted a PPK trial in 12 European healthy adults. They settled on a two-compartment model with first-order elimination, with a chain of transit compartments to model absorption. The model parameters reported for a 70 kg subject were apparent clearance of 7.7 L/hour, and central and peripheral volume of distribution of 89 L and 234 L, respectively. Although there are numerical minor differences with our analysis, (16.4 L/hour, 48.1 L, and 588 L, respectively) the PK model can be considered fully comparable. Such differences could be attributed to the different sample matrix used by Duthaler *et al.* (venous plasma and dried blood spots) and in our study (capillary blood). As in our study, body weight was also identified as the only covariate that significantly influenced the PK of ivermectin. The pharmacokinetics of ascending doses of ivermectin in *T. trichiura* infected children was studied in a similar study to this dose-finding Phase II trial.[27,28] Doses of 100 or 200 µg/kg were administered to 2–5-year-old children and doses of 200, 400, or 600 µg/kg were administered to 6–12 year-old children. In their PPK analysis, body weight was identified as the most significant covariate for clearance and volume of distribution, where the clearance per kg in the children was higher than the adults. The results are consistent with our current ivermectin PPK model, where estimated coefficient of body weight on clearance (in L) was less than weight-proportional (coefficient of 0.444 instead of 1).

The allometric exponents of weight on apparent volume and clearance were estimated in PK model of both albendazole and ivermectin. The final models show no bias on the apparent clearance and volume vs. body weight and age; thus, the final models are appropriate for estimating the PK exposure of the children and adolescents in the Phase II study. Nevertheless, the estimated allometric exponents on apparent clearance (0.302 and 0.444 for albendazole sulfoxide and ivermectin, respectively) are less than the typical value 0.75 for small molecules. Caution should be taken when they are used to extrapolate the model parameters to a lower range of body weight.

A leading advantage of the FDC formulation is being an orodispersible tablet to avoid the deaths from choking in young

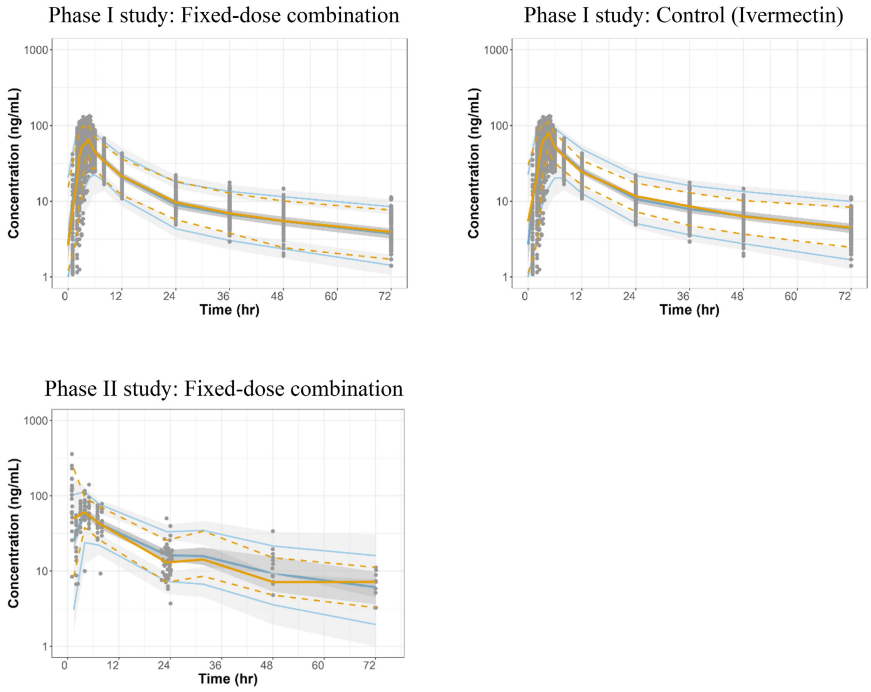

Figure 3 pcVPC for final ivermectin $H2B_{1a}$ PPK model for Phase I and Phase II studies, after the administration of either fixed-combination albendazole/ivermectin or corresponding ivermectin control. (To note: In the phase II study control ivermectin was not used). Gray dots are prediction-corrected observed concentrations. Orange dashed lines are the 95th, 50th, and 5th percentiles of the observed data. Blue lines are the 95th, 50th and 5th percentiles of the simulations. The gray shaded region indicates the 5th to 95th percentile prediction interval.

children, a usual concern in the implementation of MDA programs.[29] One concern arising from the rapid dissolution of the fixed-combination tablet in the mouth was a possible change in pharmacokinetic characteristics compared with each of the individual active substances (albendazole and ivermectin), formulated as "regular" tablets. Nevertheless, the results of the studies demonstrated that even with the orodispersible effect, the relative bioavailability of the FDC formulation was 78.5% for albendazole and 116% for ivermectin compared with the Eskazole® and Stromectol®, respectively.

The *a priori* difficulty in the development of the albendazole/ivermectin combination was that while albendazole has a fixed-dose regimen (400 mg to subjects older than 24 months, regardless of age and weight), the recommended dose for ivermectin needs to be adjusted to 0.15–0.4 mg/kg body weight. To account for the need to ivermectin dose adjustment based on body weight, a 400/9 mg FDC tablet was designed for children under 45 kg and a 400/18 mg FDC tablet was designed for adolescents or adults ≥ 45 kg. The current analyses confirm that this simple weight-based FDC regimen achieves desirable albendazole and ivermectin levels in both children and adolescents in the Phase II trial.

The exploratory E–R analysis of the CR of *T. trichiura* was done to confirm that the dose selected was appropriate for the phase III trial. The efficacy results were collected from children and adolescents treated with a narrow dose range of 400 mg albendazole and 9 or 18 mg ivermectin, therefore, a full E–R analysis of efficacy was not attempted and the impact of baseline covariates on the E–R relationship was not evaluated.

The Phase II trial was not designed to evaluate the efficacy since the sample size was too low to obtain a powered enough conclusion. Still, the main efficacy variable, CR, shows a clear trend to indicate

Table 5 Comparison of albendazole and ivermectin AUC between phase I and phase II trials

Study	Drug administered	Albendazole sulfoxide	Ivermectin $H2B_{1a}$
Phase I	FDC × 1 day	4,310 (1630)	1,370 (433)
	Albendazole-Control (Eskazole®)	5,490 (2080)	N.A.
	Ivermectin-Control (Stromectol®)	N.A.	1,180 (369)
Phase II	FDC × 1 day	5,780 (1650)	1,360 (402)
	FDC × 3 days	5,650 (1500)	1,170 (382)
	Albendazole-Control (Eskazole®)	7,300 (2040)	N.A.

AUC was AUC_{0-inf} (ng h/mL) of day 1 dose; Values are reported as mean (Standard Deviation); N.A., not applicable.

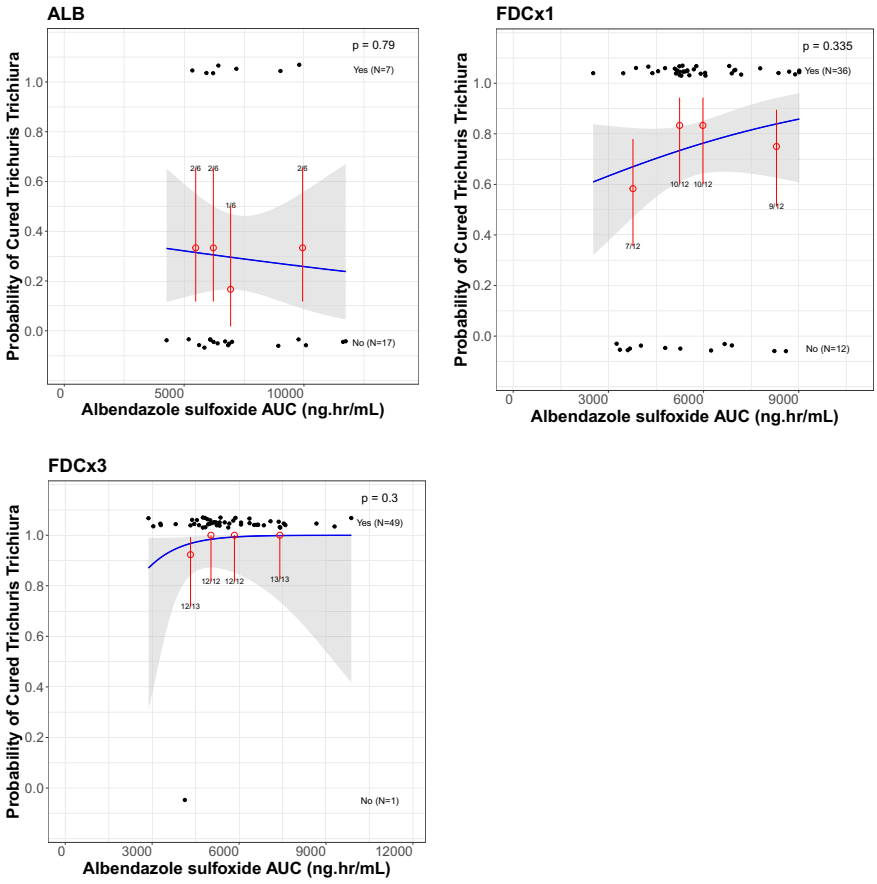

Figure 4 Exposure–response relationship of CR for *T. trichiura* and albendazole in phase II trial. "Yes" and "No" in the figure refer respectively to if subjects were cured or not cured for *T. trichiura*. Subjects are stratified into exposure quartiles. Red points are the CR per exposure quartile plotted at the median exposure per quartile. Vertical red bars are 90% confidence intervals of the CR. Gray band represents the 5th to 95th percentile confidence interval of a linear logistic regression fit. The *P*-value is the significance level of the slope of the logistic regression fit using a *z*-test. AUC was calculated for the first dose using the empirical Bayes estimates of the PK parameters of the PPK model.

a higher efficacy after the administration of FDC compared with the control (albendazole) against *T. trichiura*. Conversely, the Phase II trial was designed to evaluate the safety of ivermectin in children after FDC since the ivermectin exposure was anticipated to be slightly higher than the typical recommended dose. Results of the Phase II trial suggest that the FDC regimens are safe for

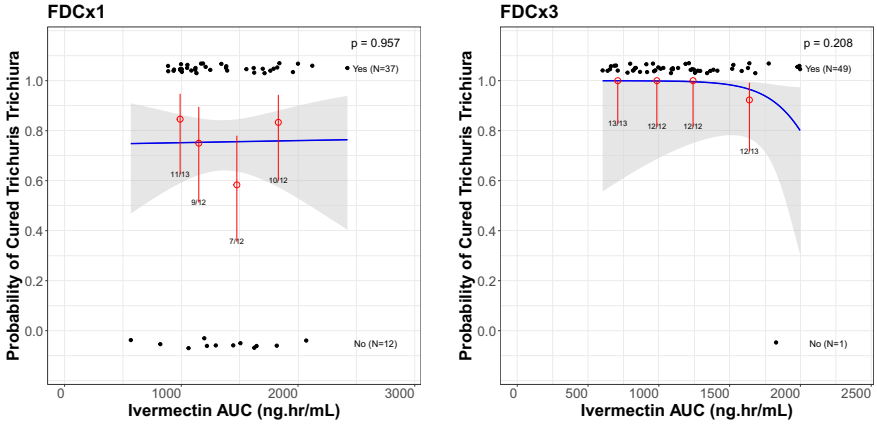

Figure 5 Exposure–response relationship of CR for *T. trichiura* and ivermectin in Phase II trial. "Yes" and "No" in the figure refer respectively to if subjects were cured or not cured for *T. trichiura*. Subjects are stratified into exposure quartiles. Red points are the CR per exposure quartile plotted at the median exposure per quartile. Vertical red bars are 90% confidence intervals of the CR. Gray band represents the 5th to 95th percentile confidence interval of a linear logistic regression fit. The *P*-value is the significance level of the slope of the logistic regression fit using a *z*-test. AUC was calculated for the first dose using the empirical Bayes estimates of the PK parameters of the PPK model.

children and could achieve high CR for *T. trichiura* infections. The results confirmed that the dosage selected in the phase II trial was appropriate for the subsequent phase III clinical trial.

This PPK study merged data from the Phase I and Phase II trials, part of the clinical development program of the albendazole/ivermectin FDC, that is intended to treat STH, particularly *T. trichiura*. The study describes the pharmacokinetic characteristics of albendazole sulfoxide and ivermectin $H2B_{1a}$ in children and adults. In both analytes, the clearance and volume of distribution increased with body weight, but no effect was observed with other covariates. The bioavailability obtained with the FDC is similar to the individual products, in all ages. Results confirmed that the dosage selected in the Phase II trial was appropriate for the subsequent phase III of the clinical trial. In summary, this study provides valuable PK information on the albendazole/ivermectin fixed-combination orodispersible tablet that together with the emerging safety and efficacy data appears as a promising contribution to STH control in endemic countries.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

J.A. is an employee of Laboratorios Liconsa. Nonetheless, the authors declare that the clinical was conducted in the absence of commercial or financial relationships that could interfere with the results or interpretation. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

J.A. wrote the manuscript. J.A., S.K., A.K., C.M., and J.M. designed the research. S.K., C.M., T.A, and A.K. performed the research. H.L., J.G., and P.F. analyzed the data.

ETHICS STATEMENT

This manuscript includes the pharmacokinetic analysis of a phase I and a phase II trial. As stated on the text, both studies were authorized by the corresponding Ethic's Committee and Health Authority. The trials were registered (number provided on the text) and conducted in agreement with Helsinki, GCP and applicable local law.

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