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Novel Patient-Friendly Orodispersible Formulation of Ivermectin is Associated With Enhanced Palatability, Controlled Absorption, and Less Variability: High Potential for Pediatric Use

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Abstract

Ivermectin has been used since the 1980s as an anthelmintic and antiectoparasite agent worldwide. Currently, the only available oral formulation is tablets designed for adult patients. A patient-friendly orodispersible tablet formulation designed for pediatric use (CHILD-IVITAB) has been developed and is entering early phase clinical trials. To inform the pediatric program of CHILD-IVITAB, 16 healthy adults were enrolled in a phase I, single-center, open-label, randomized, 2-period, crossover, single-dose trial which aimed to compare palatability, tolerability, and bioavailability and pharmacokinetics of CHILD-IVITAB and their variability against the marketed ivermectin tablets (STROMECTOL) at a single dose of 12 mg in a fasting state. Palatability with CHILD-IVITAB was considerably enhanced as compared to STROMECTOL. Both ivermectin formulations were well tolerated and safe. Relative bioavailability of CHILD-IVITAB compared to STROMECTOL was estimated as the ratios of geometric means for C_{max}, $AUC_{0-\infty}$, and $AUC_{0\text{-last}}$, which were 1.52 [90% CI: 1.13-2.04], 1.27 [0.99-1.62], and 1.29 [1.00-1.66], respectively. Maximum drug concentrations occurred earlier with the CHILD-IVITAB formulation, with a median T_{max} at 3.0 h [range 2.0-4.0 h] versus 4.0 h [range 2.0-5.0 h] with STROMECTOL ($P = .004$). With CHILD-IVITAB, variability in exposure was cut in half (coefficient of variation: 37% vs 70%) compared to STROMECTOL. Consistent with a more controlled absorption process, CHILD-IVITAB was associated with reduced variability in drug exposure as compared to STROMECTOL. Together with a favorable palatability and tolerability profile, these findings motivate for further clinical studies to evaluate benefits of such a patient-friendly ODT formulation in pediatric patients with a parasitic disease, including infants and young children <15 kg.

Keywords

bioavailability, children, ivermectin, orodispersible formulation (ODT), palatability, pharmacokinetics, STROMECTOL, TIP-based technology, variability

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Introduction

Ivermectin has been used since the 1980s as an oral antiparasitic agent for many indications.[1] It is effective in treating parasitic diseases such as onchocerciasis, lymphatic filariasis, strongyloidiasis, head lice, intestinal nematodes, and scabies.[2–4] The burden of these diseases is high, particularly in children younger than 5 years in low- and middle-income countries (LMICs).[5] The importance of oral ivermectin for numerous neglected tropical diseases is well established, placing it on the WHO List of Essential Medicines for Children for treatment of ectoparasitic, filarial, and intestinal helminth infections.[6] Through a national survey of clinicians of different specialties managing children with scabies in Switzerland, there was a call to give high priority to research on child-friendly treatment modalities.[7] Currently approved and commercially available ivermectin formulations such as STROMECTOL are listed in the WHO referenced "Drug Bank Online."[8] Furthermore, an oral form recently authorized in Switzerland[9] is also only available as a tablet designed for adults. In children <6 years currently available ivermectin formulations need to be administered as crushed tablets or in a suspended form, both prone to imprecise dosing (loss of product after crushing or sedimentation of product after suspension).[10–13] They are also not palatable, and thereby predisposed to be expelled out of the mouth by children. When available, oral liquid medicinal product formulation is a common alternative to solid oral dosage forms to ease medicine administration.[13] In Latin America, a liquid oral ivermectin formulation has been manufactured and used in trials for treatment of young children with head lice in Colombia,[14,15] and myiasis in Peru.[16] Nevertheless, this liquid oral formulation has been discontinued since. In Germany, a liquid oral ivermectin formulation was developed, but not evaluated in trials.[17] However, oral liquid formulations are suboptimal in infants and toddlers.[18] Aside from poor palatability, ivermectin as a suspension is not viable in clinical practice as the stability is fragile, the shelf life is short (2-3 weeks),[17] and the suspension is affected by UV light exposure.[4] For these reasons, such formulations are not desirable for the hot and humid tropical conditions found in a majority of LMICs. All the above compromise drug adherence and effectiveness of prevention and treatment of parasitic diseases with ivermectin, particularly in young children and infants.

It should be noted that safety of ivermectin in young children <15 kg and pregnant women has not been evaluated in clinical studies so far. Owing to its high effectiveness against different diseases and lack of alternative child-friendly modalities, it is nevertheless frequently administered as crushed tablets off-label in these sensitive populations, and is prone to dosing errors associated with efficacy and safety risks.[19–21]

An appropriate pediatric ivermectin formulation, which can be readily used in the clinic and mass drug administration settings in LMICs, has not yet been developed nor clinically evaluated. For a child-friendly drug delivery strategy, orodispersible tablets (ODT) in the form of inorganic particulate drug carriers can be used as multifunctional excipients offering a potential solution to address unique medical needs in infants and children, while maintaining a favorable excipient safety and acceptability profile in these vulnerable patient populations.[22] A recent study has shown such novel orodispersible formulation, used as placebo ODT with food-grade orange aroma, to be well accepted by children.[23] A promising drug delivery device, namely multifunctional template inverted particles (TIP) microcapsules loading an active ingredient, has been developed for ivermectin. It is expected to enable fast oral disintegration associated with rapid and controlled drug absorption and enhanced taste masking.[24]

High interindividual variability in drug exposure with STROMECTOL has been highlighted in previously published studies.[25] Ahead of testing this novel TIP-based ivermectin mini ODT (CHILD-IVITAB) in children, a clinical study is warranted with specific interest in investigating the variability in ivermectin absorption and pharmacokinetics with CHILD-IVITAB as compared to STROMECTOL in healthy adults, in addition to evaluating its palatability and tolerability. The overall goal of this project is to develop a child-friendly ivermectin formulation for pediatric patients with a parasitic disease including infants and children <15 kg.

Methods

The study (Clinicaltrials.gov: NCT05477810) was conducted in the Service of Clinical Pharmacology at the University Hospital in Lausanne, Switzerland, in accordance with the Declaration of Helsinki and its amendments, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and applicable regulations and laws. The clinical study protocol, case report form, and informed consent forms, were approved by the local Ethics Committee (Commission cantonale d'éthique de la recherche sur l'être humain du Canton de Vaud, CER-VD, study Nr. 2022-01276) and the national regulatory authority (Swiss Agency for Therapeutic Products, Swissmedic, authorisation number 102684116) under the sponsorship of the University Children's Hospital (UKBB), Basel. Consent to participate was obtained from all study participants.

Study Design and Subjects

Eligible study subjects were healthy male and female adults aged between 18 to 45 years, with a body mass index of 18-30 kg/m^2. A difference in sex representations between male and female study subjects within 1/3-2/3 was anticipated. Exclusion criteria included history or evidence of clinically significant disease or conditions, significant laboratory abnormality including hepatitis or HIV serology, recent history of alcohol or drug abuse, pregnancy or breastfeeding, and recent acute disease or use of medication the week prior to the study.

This clinical pharmacology study was a phase I, single-center, open-label, randomized, 2-period, 2-way crossover, single-dose PK study in which the active substance ivermectin was administered as a single dose of 12 mg (as 4 tablets of 3 mg) as either CHILD-IVITAB or STROMECTOL, in fasting conditions. Both periods were to be separated by a washout period of at least 7 days (considering that 97% of the drug is eliminated after 5 half-lives, 5×18 h[26] $= 90$ h).[27] Palatability, tolerability, safety, pharmacokinetics, and its variability were assessed in 16 healthy subjects. During each period, plasma samples (EDTA tubes) were collected predose, at 30 min, and at 1, 2, 3, 4, 5, 6, 8, 10, 24, 48, 72, and 96 h postdose. Plasma was centrifuged and stored as per protocol at −20°C until bioanalytical analysis.

CHILD-IVITAB, a TIP-Based Ivermectin ODT

Previous studies have shown that porous calcium phosphate and carbonate carriers are well accepted in adults and children 2-10 years old, revealing that the disintegration of such tablets leads to a pleasant mouthfeel.[23,28] In order to formulate the CHILD-IVITAB, the novel excipient TIP was used.[24] In contrast to traditional porous calcium carbonate carriers, such as functionalized calcium carbonate, TIP is a monomaterial.[24] The microcapsules consist of pure hydroxyapatite, a naturally occurring mineral recognized as a primary constituent of bone. Hydroxyapatite is listed in the United States Pharmacopeia (USP) and European Pharmacopeia (Ph. Eur.), is biodegradable, is generally recognized as safe, and is widely accepted as a food additive.[29–31] The particles have an average size of 20 #x000B5;m and feature a hollow inner cavity, which serves as the drug encapsulation space. Previous work has shown that ivermectin can be loaded into the hollow cavity of TIP, highlighting that TIP is a self-loading microcapsule.[24] The hollow cavity of TIP is enclosed by a porous shell, which is responsible for an excellent wettability and rapid water uptake. Upon contact with water, TIP tablets therefore disintegrate within a few seconds into primary particles. In combination with its good compactability to hard tablets, TIP is thus a promising platform technology for the formulation of ODT, enabling age-appropriate drug delivery.[24] The CHILD-IVITAB tablets have a diameter of 5 mm, weigh a total of 60 mg, contain 3 mg of ivermectin, and disintegrate in less than 20 s.

Ivermectin drug substance was provided by Pharmaserv AG (Stansstad, Switzerland) and was analyzed in compliance with European Pharmacopoeia current edition (Ph. Eur. 11.0, Ivermectin p3155-3158). CHILD-IVTAB ODTs were produced under GMP at the Hospital Pharmacy of the University Hospital Basel. Content of ivermectin as CHILD-IVITABs and STROMECTOL was quantitatively determined and did comply with compendial acceptance values. Consistency of dosage units and drug substance content was demonstrated under GMP using a validated HPLC method as defined by the ivermectin monograph of the Ph. Eur. (11.0/1336). For STROMECTOL, the corresponding analysis was carried out by the commercial supplier.

Tablets were stored under controlled conditions in a temperate closet at 20-25°C. Shelf life was at least 18 months as determined by 6 month accelerated stability tests carried out at 25, 35, and 45°C according to ICH guideline Q1A(R2). STROMECTOL was provided by the Hospital Pharmacy of the University Hospital Basel (manufacturer MERCK; batch number W002864).

Study Drug Administration

Subjects were in a fasting state from at least 8 h prior to and up to 4 h after drug intake, no water was allowed during the hour prior to study drug intake. CHILD-IVITAB was directly extracted from a sealed glass storage container and given to each subject (at time 0). Subjects were instructed to place 4 CHILD-IVITAB tablets between the gum and the cheek for 30 s, then rinsed and swallowed with 150 mL of water. STROMECTOL tablets were immediately swallowed with 150 mL of water (at time 0). Block randomization of treatment sequence allocation stratified by sex was done (3 blocks of length 6, 2, 2 for each sex group) and blinding was held up to time of drug dispensing.

Bioanalytical Analysis

Plasma ivermectin samples were quantified by liquid chromatography tandem mass spectrometry (LC-MS/MS).[32] The methodology for the bioanalytical assay for plasma and blood samples is described in detail in Duthaler et al.[32] The method was validated according to the guideline on bioanalytical method validation of the European Medicines Agency (EMA).[32] The limit of quantification (LOQ) of ivermectin plasma samples was 0.5 ng/mL. The method

was linear, accurate, and precise over concentrations ranging from 0.5 to 250 ng/mL for plasma. Quality control samples were analyzed throughout the study to determine intra- and interassay precision and accuracy of the analysis. Incurred sample reanalysis of plasma samples (n = 64) showed a maximum bias of 12.7%. Overall, the analyses met the acceptance criteria outlined in regulatory guidelines.

Pharmacokinetic Analysis

As primary analysis, pharmacokinetic parameters were estimated for the novel CHILD-IVITAB formulation and for the marketed STROMECTOL using a noncompartmental analysis. Ivermectin plasma concentration measurements were performed in duplicates for quality purpose. Maximum plasma concentration (C_{max}) and time to maximum plasma concentration (t_{max}) were obtained directly from the plasma concentration–time profiles. The area under the plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$) of ivermectin in each treatment period were calculated post hoc using the linear up log down method. Actual time after last dose was used. Apparent clearance (CL/F) and apparent volume of distribution (V/F) during the terminal elimination phase were calculated using the following formulae: CL/F = Dose / $AUC_{0-\infty}$ and V/F = CL / λ_z (where λ_z is the terminal elimination rate constant). Bioavailability of the CHILD-IVITAB formulation relative to STROMECTOL tablets (F_{rel}) following a single oral administration was calculated based on geometric mean values of $AUC_{0-\infty}$, AUC_{0-last}, and C_{max}. Descriptive PK parameters were compared between formulations using a paired t-test on log-transformed values.[33] As a sensitivity analysis, the difference in AUC_{0-inf}, AUC_{0-last}, and C_{max} between formulations at the individual level was calculated.

The sample size calculation stipulated that bioequivalence was considered as established based on the geometric means of $AUC_{0-\infty}$ in individual study subjects, with a difference between the 2 ivermectin formulations and a 90% confidence interval around it entirely contained in the usual ranges of 80%-125% for $AUC_{0-\infty}$. Statistical methodology, including the analysis plan and sample size calculation, are summarized in the supplementary material (Supplement: Text Methodology S1).

To inform studies in pediatric patients, bioavailability between the 2 ivermectin formulations were compared applying the official bioequivalence (BE) criteria of 80%-125% for AUC_{0-inf} and AUC_{0-last}, as defined by Regulatory Agencies in Europe and the United States.

Pharmacokinetic calculations were performed using the Phoenix WinNonLin software (version 8.4.0). The dataset was created using SAS 9.4. Other statistical analysis was undertaken using the software package STATA (StataCorp. 2017. Stata Statistical Software: Release 17. College Station, TX: StataCorp LP).

Palatability, Tolerability, and Safety Assessments

Palatability, tolerability, and safety were evaluated using visual analog scales (VAS). VAS applied a 10 cm scale from 0 (no complaint) to 10 cm (worse possible complaint) at regular time intervals, except for overall palatability for which 5 cm was considered to be neutral, with values under 5 cm representing a good taste and values above 5 cm taste deterioration.[33]

VAS for palatability was performed predose, at 2, 5, 10 and 30 min after intake to evaluate the intensity, sweetness, bitterness, and overall palatability. Typical adverse events with an emphasis on known gastrointestinal (GI) (nausea and abdominal pain) and central nervous system (CNS) symptoms (sedation/drowsiness, dizziness, anxiety, subjective concentration capacity, headache, and fatigue) were followed over 10 h (predose, at 30 min and 1, 2, 3, 4, 6, and 10 h after drug intake). Ivermectin has not been associated with any significant toxicity to the liver, kidney, heart, or blood. Biochemistry and hematology parameters were measured at screening and on day 5 of period 2. Vital signs and serial electrocardiograms (ECGs) were also performed predose, at 2 and 4h postdose, as a routine precautionary safety measure. QT intervals corrected according to the Bazett formula were measured.

Results

Study Subjects

Median age (± SD) was 24.0 (IQR 20.8-28.0) years and median body weight was 63.7 (IQR 58.0-71.6) kg. Mean administered dose of ivermectin was 0.19 (IQR 0.17-0.21) mg/kg. The washout period was standardized to 14 days for all subjects for practical purposes and to reproduce a standard ivermectin therapeutic regimen.

Palatability, Tolerability, and Safety

Palatability of the ivermectin CHILD-IVITAB formulation was particularly enhanced during the first 15 min after dose administration and was characterized by a sweet and intense pleasant taste, which differed from the neutral taste of STROMECTOL tablets (Figure 1). Both formulations lacked bitterness. Residues from undissolved CHILD-IVITABs after 30 s were reported by most subjects and may in part be explained by a dry mouth. Subjects were not allowed to drink during the hour prior drug dispensing in order to standardize drug intake. They described further fast dissolution and easy swallowing of these residues with the rinsing and

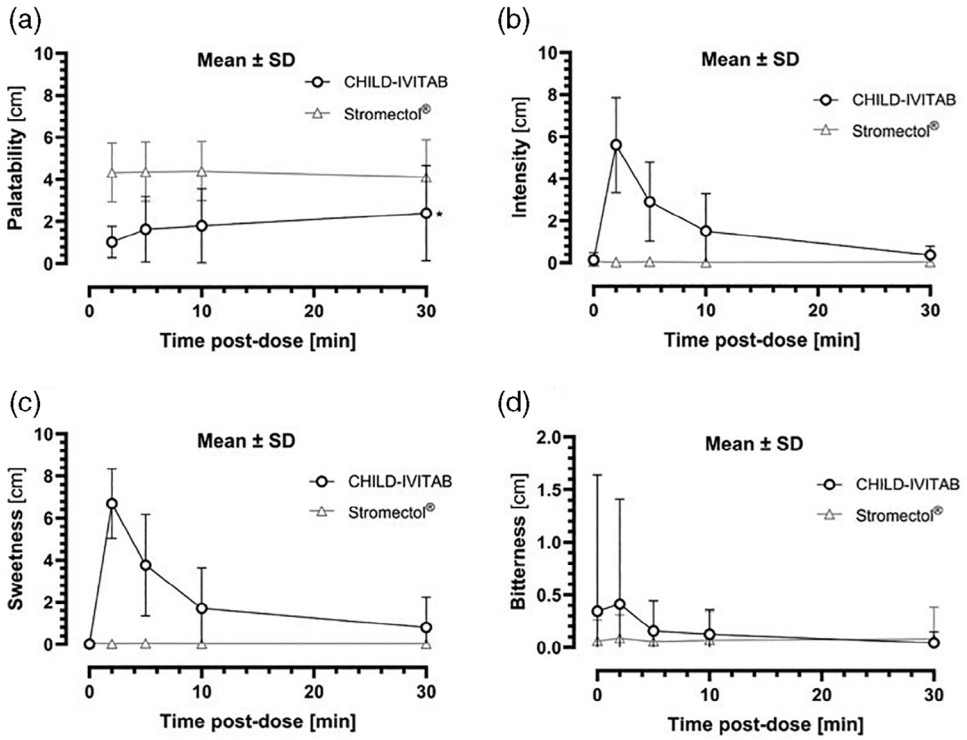

Figure 1. Evaluation of taste of different formulations of ivermectin according to visual analogue scales regarding intensity, sweetness, bitterness (all 3 items: 0 for absence and 10 cm for extreme intensity) and overall palatability (5 cm as neutral, perceived as pleasant if <5 cm and as poor if >5 cm). CHILD-IVITAB (open circles) and STROMECTOL tablets (open triangles) are represented.

Table 1. Pharmacokinetic Parameters of Ivermectin According to Formulation (Noncompartmental Analysis, 16 Subjects per Formulation).T_{max} Shown as Median (Range). All Other Values Are Geometric Mean (CV%). CV Is Calculated as $\mathbf{CV} = \sqrt{e^{\omega^2} - 1}$ (ω, Standard Deviation)

Ivermectin Formulation	t_{max} [h]	C_{max} [ng/mL]	$AUC_{(0,last)}$ [ng•h/mL]	$AUC_{(0,\infty)}$ [ng•h/mL]	$t_{1/2}$ [h]	CL_{Tot}/F [L/h]	V_z/F [L]
Ivermectin ODT	3.0 (2.0-4.0)	52.0 (33)	881 (35)	1090 (37)	46.3 (39)	11.0 (37)	738 (50)
STROMECTOL	4.0 (2.0-5.0)	35.4 (78)	707 (75)	885 (70)	46.6 (37)	13.6 (70)	911 (89)

t_{max} is a median (range). All other values are geometric mean (CV%).

swallowing of 150 mL of water given as per protocol 30 s after drug intake. No major adverse events were reported during the study. The most common adverse event reported was headache (n = 8), most often attributed to study conditions although a contribution of ivermectin cannot be entirely ruled out. Safety and tolerability assessments using GI and CNS VAS did not disclose significant difference between STROMECTOL and the CHILD-IVITAB. (Figures S1 and S2: GI and CNS VAS). Biochemistry and hematology parameters measured at screening and on day 5 of period 2 showed no significant change in laboratory parameters during the study. However, the limited follow-up precludes from an assessment of a trend between formulations. No trend was noted on ECG intervals, nor on vital signs. Both formulations were very well tolerated.

Pharmacokinetics and its Variability

Ivermectin plasma concentrations were measured after the administration of single 12 mg oral dose of the CHILD-IVITAB formulation and the marketed tablets STROMECTOL (Merck). In line with the sample size calculation, a total of 16 subjects (7 female and 9 male) completed the study. No drop-out occurred.

Pharmacokinetic parameters of ivermectin for each formulation are shown in Table 1 and plasma concentration–time profile in Figure 2. Results for duplicated concentrations were similar (data not shown). Maximum concentration (C_{max}) occurred earlier with the CHILD-IVITAB formulation, with a median T_{max} of 3 h [range 2-4 h] versus 4 h [range 2-5 h] for STROMECTOL ($P = .004$); and higher peak ivermectin plasma concentrations (C_{max}, %CV) were observed with CHILD-IVITAB, with a geometric

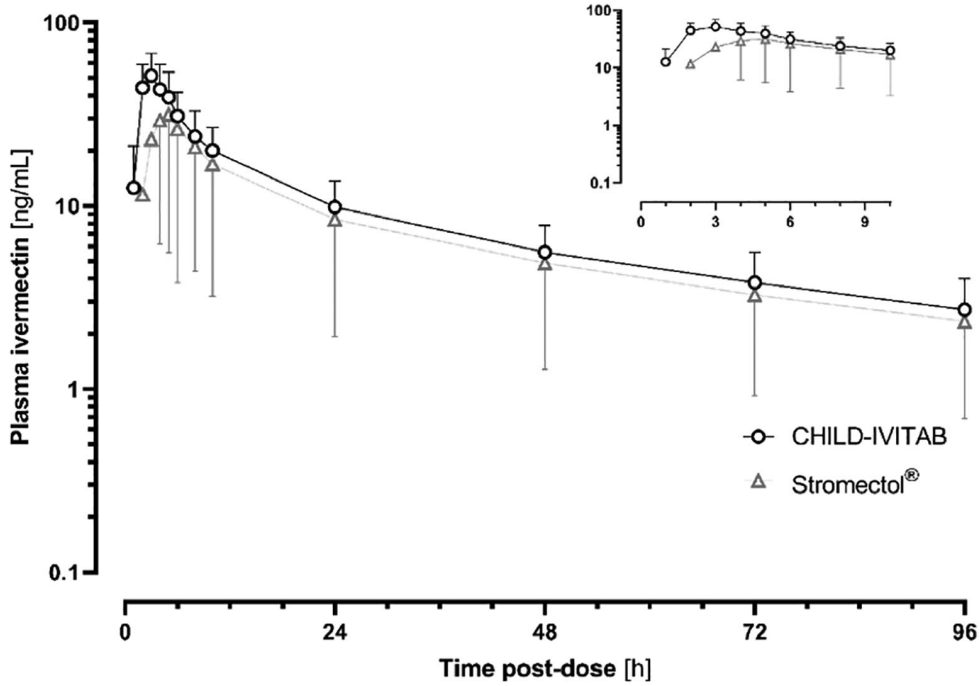

Figure 2. Time profile of geometric mean plasma concentration with log-SD plasmatic ivermectin concentrations according to formulation (shown as 1-sided error bars). CHILD-IVITAB (open circles) and STROMECTOL (open triangles) are represented. Details of the concentrations during the first 10 h are shown on the insert.

mean of 52.0 (95% CI: 44.5-60.8, CV = 33%) ng/mL versus 35.4 (95% CI: 25.3-49.6, CV = 78%) ng/mL with STROMECTOL. Apparent clearance (CL/F, %CV) was similar with CHILD-IVITAB with a geometric mean of 11.0 (37%) L/h versus 13.6 (70%) L/h with STROMECTOL. Volume of distribution (V_z/F) was 738 (50%) L with CHILD-IVITAB and was similar for both formulations (P = .3). Half-life ($t_{1/2}$) was 46 h with both formulations (P = 1). Total ivermectin exposure ($AUC_{0\text{-}\infty}$ and $AUC_{0\text{–last}}$) was marginally higher with CHILD-IVITAB, with, respectively, 1090 (95% CI: 917.4-1295.8, CV = 37%) ng·h/mL versus 885 (95% CI: 651.6-1211.4, CV = 70%)) ng·h/mL with STROMECTOL (P = .6) for $AUC_{0\text{-}\infty}$ and 881 (35%) versus 707 (75%) with STROMECTOL for $AUC_{0\text{-last}}$. Variability in exposure (coefficient of variation) was cut in half with CHILD-IVITAB as compared to STROMECTOL (37% vs 75%).

It should be noted that with the 96-h sampling, extrapolation of $AUC_{0\text{-}\infty}$ was > 20% in 9 individuals, which limits reliability of this calculation. For this reason, $AUC_{0\text{-last}}$ is also reported.

A marginal carry-over effect was observed in 5 subjects with very low yet quantifiable ivermectin plasma concentrations before the second period dose administration.

Relative bioavailability of CHILD-IVITAB compared to STROMECTOL (F_{rel}) was estimated as ratios. The mean log-transformed estimates were of 1.27 [90% CI: 0.99-1.62], 1.29 [1.00-1.66], and 1.52 [1.13-2.04], for $AUC_{0\text{-}\infty}$, $AUC_{0\text{-last}}$, and C_{max}, respectively. The stated conditions to establish bioequivalence were not met.

As study participant #14 showed substantially lower ivermectin concentrations following STROMECTOL (Figure S3 and Table S1) than all other study subjects, a sensitivity analysis was performed without this individual. Exposure with STROMECTOL was slightly higher (and variability in exposure reduced) while that with CHILD-IVITAB was similar in this sensitivity analysis as compared to the reference analysis with all study subjects (Table 2 and Figure S3). Without individual #14, relative bioavailability of CHILD-IVITAB compared to STROMECTOL (F_{rel}) was estimated as the ratio of $AUC_{0\text{-}\infty}$, $AUC_{0\text{-last}}$, and C_{max}. The mean log-transformed estimates were 1.17 [0.93-1.47]%, 1.18 [0.93-1.48]% and 1.37 [1.04-1.79]%, respectively.

Discussion

This study has demonstrated that this novel ivermectin ODT formulation (CHILD-IVITAB) based on TIP technology has the potential for pediatric use, as it is well tolerated and shows enhanced palatability.

Table 2. Pharmacokinetic Parameters of Ivermectin According to Formulation (n = 15 Study Subjects Per Formulation, Excluding Outlier Subject #14). T_{max} Shown as Median (Range). All Other Values Calculated as Geometric Mean (CV%). CV Is Calculated as $\mathbf{CV} = \sqrt{e^{\omega^2} - 1}$

Ivermectin Formulation	t_{max} [h]	C_{max} [ng/mL]	$AUC_{(0,last)}$ [ng·h/mL]	$AUC_{(0,\infty)}$ [ng·h/mL]	$t_{1/2}$ [h]	CL_{Tot}/F [L/h]	V_z/F [L]
Ivermectin ODT	3.0 (2.0-4.0)	51.6 (34)	899 (35)	1100 (37)	45.1 (39)	10.9 (37)	710 (49)
STROMECTOL	4.0 (2.0-5.0)	39.0 (64)	793 (54)	973 (56)	44.2 (31)	12.3 (56)	787 (54)

t_{max} is a median (range). All other values are geometric mean (CV%).

CHILD-IVITAB demonstrated more controlled absorption associated with considerably reduced interindividual variability and close to equivalent exposure coverage as compared to STROMECTOL. Consistent with a faster absorption process, time to peak drug concentration (T_{max}) was reduced by 1 h with CHILD-IVITAB and mean C_{max} was increased by 47% (with lower interindividual variability) as compared to STROMECTOL. PK curves are almost identical after the initial absorption phase (i.e., first 3-4 h after drug administration), with considerably reduced variability, cutting the coefficient of variation in half with CHILD-IVITAB as compared to STROMECTOL. Highly variable exposure with the original, conventional ivermectin tablet[34,35] may also have contributed to differences in exposure between tested CHILD-IVITAB designed for children and STROMECTOL. This is supported by a sensitivity analysis without individual #14 who had very low exposure with STROMECTOL, showing a markedly reduced difference in $AUC_{0\text{-last}}$ (13% instead of 25%) and C_{max} (32% instead of 47%).

Consistent with these findings, any difference in AUC was driven by a faster and more controlled absorption process associated with CHILD-IVITAB, which in turn is likely a result of faster dissolution associated with partial intraoral, transmucosal drug absorption, and/or bypassing a first-pass effect. Ivermectin is characterized by a wide therapeutic safety margin. According to STROMECTOL summary of product characteristics (SmPC), the usual ivermectin dose is 0.2 mg/kg, that is, an oral dose of 12 mg in a 60 kg adult.[26] Higher dosage has also been evaluated in some indications, such as *Wuchereria bancrofti* microfilaremia, where ivermectin dose can be increased up to 24 mg (0.4 mg/kg); even higher dosage up to 2 mg/kg were investigated and well tolerated.[36] Accordingly, higher C_{max} values with CHILD-IVITAB (52.0 vs 35.4 ng/mL) are not expected to raise any clinically relevant safety issues. In terms of efficacy, a faster and more controlled absorption process with CHILD-IVITAB is expected to exhibit at least similar efficacy as compared to conventional ivermectin formulations such as STROMECTOL. To further mitigate any negative effect of a higher C_{max}, it will be considered to administer CHILD-IVITAB like other ivermectin tablets (e.g., with immediate water intake) to minimize differences in C_{max} making the overall exposure coverage even more similar in future pediatric studies.

Interestingly, a half-life of approximately 46 h, significantly longer than the 18 h reported by the manufacturer of STROMECTOL, was observed for both formulations in this study. A longer follow-up of 96 h postdose may explain this result, as a similar or longer half-life is also reported in other PK studies.[34,37] Newer analytical technologies may also have contributed to this observation in lowering the limit of detection and quantification of ivermectin since marketing and allowing to better characterize the late elimination phase. Nevertheless, a 14-day washout period should have been sufficient to allow elimination of 99% of ivermectin considering the 46 h half-life. Despite this, the reliably of $AUC_{0\text{-}\infty}$ extrapolation based on the 96-h sampling should be regarded with some caution. A longer washout period would be recommended in future crossover studies with ivermectin.

Ivermectin is a highly lipophilic compound, of relatively high molecular weight (875 g/mol), which is a substrate of the P-glycoprotein (P-gp) and is moderately well absorbed. High interindividual variability in exposure was reported in previously published PK studies (with CV ranging from 30% to 44%).[25,34,35,38,39] A food effect was described, with an increased bioavailability (ranging from 18% to 25%) after the administration of 12 mg of ivermectin with a high-fat meal.[40,41] Bile secretion with increased dissolution of the ivermectin tablet is thought to drive this food effect. In this study, ivermectin was administered under fasting conditions, as recommended by the manufacturer, which may have contributed to an increase in the interindividual variability in exposure to STROMECTOL. It is also conceivable that the limited ivermectin absorption in the fasting state had less impact on average ivermectin bioavailability with the CHILD-IVITAB than with STROMECTOL, given the possible absorption of a fraction of the dose through the oral mucosa.

It should also be noted that CHILD-IVITAB based on the TIP technology is stable in hot and humid atmosphere and no external agent is required for taste masking and no water intake is needed for swallowing. It represents a promising alternative oral formulation

for pediatric patients, including young children in LMICs.

Conclusion

The TIP-based ivermectin formulation CHILD-IVITAB showed controlled absorption associated with reduced variability in drug exposure as compared to STROMECTOL. Together with a favorable palatability and tolerability profile, these findings will propel further clinical studies to evaluate the child-friendly ODT formulation CHILD-IVITAB. Clinical trials are being set-up in Europe and LMICs to assess palatability, tolerability, safety, efficacy, and exposure coverage of CHILD-IVITAB in pediatric patients with a parasitic disease, including infants and young children <15 kg.

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Author Contributions

Michael Buettcher, Marc Pfister, Jörg Huwyler, Laura E. Rothuizen, Kim Dao, and Thierry Buclin designed the study, while Kim Dao, David Haefliger, Monia Guidi, Carine Bardinet, Haithem Chtioui, Abdelwahab Boulekbache, Laura E. Rothuizen, and Thierry Buclin performed the study and interpreted data. Andreas Schittny and Jonas Kost developed and manufactured the study formulation as part of their PhD thesis projects. Urs Duthaler analyzed the plasma and whole blood samples. Kim Dao, Urs Duthaler, Marc Pfister, Thierry Buclin, and Monia Guidi contributed to PK analysis. Kim Dao, Thierry Buclin, Andrew Atkinson, and Klervi Golhen performed statistical analysis, and Kim Dao, Michael Buettcher, Laura E. Rothuizen, Klervi Golhen, and Marc Pfister drafted the manuscript. All authors critically reviewed and approved the manuscript.

Conflicts of Interest

Authors have no reported conflict of interest. Marc Pfister and Jörg Huwyler are members of the board of Galvita AG.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplemental Information

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