**Efficacy, safety and acceptability of ascending doses of ivermectin in combination with albendazole for *Trichuris trichiura* infections in preschool-aged children: a single-blind randomised controlled dose-ranging trial**

**NCT Number: NCT06184399**

**Document date: 08 May 2024**

# Efficacy, safety and acceptability of ascending doses of ivermectin in combination with albendazole for *Trichuris trichiura* infections in preschool-aged children: a single-blind randomised controlled dose-ranging trial

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| **Funding Agency** | Swiss National Science Foundation | | |

# 1. General information

## I. List of investigators and other persons involved

| Title | Names | Institution | Position | Function in trial |
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| MSc | Said Mohammed Ali | Public Health Laboratory Ivo de Carneri (PHL-IdC) Foundation, Pemba, Tanzania | CEO | Co-PI |
| BSc | Fauz Abdi | Public Health Laboratory Ivo de Carneri (PHL-IdC) Foundation, Pemba, Tanzania | In-charge Lab services | Lab lead |
| Dr. | Ibrahim Said Mohammed | Ministry of Health, Pemba, Tanzania | Project leader, physician | Study physician |
| MSc | Viviane Sprecher | Swiss TPH, Allschwil, Switzerland | Doctoral student | Co-PI, Study pharmacist |
| MSc | Annina Schnoz | Swiss TPH, Allschwil, Switzerland | Doctoral student | Co-PI |
| Dr. | Jan Hattendorf | Swiss TPH, Allschwil, Switzerland | Project leader | Statistician |

## II. Signatures

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I have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and will complete the trial within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this trial. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the trial.

I will use only the informed consent forms approved by the Sponsor or its representative and will fulfil all responsibilities for submitting pertinent information to the Independent Ethics Committees responsible for this trial.

I agree that the Sponsor or its representatives shall have access to any source documents from which Case Report Form information may have been generated.

**Co-Principal investigator**

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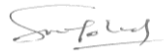
| Signature & Date |  |
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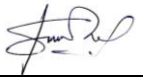
| Signature & Date |  |
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## III. Abbreviations

| | |
|---|---|
| AE | Adverse event |
| CI | Confidence interval |
| CR | Cure rate |
| CRF | Case report form |
| EKNZ | Ethikkommission Nordwest- und Zentralschweiz |
| EPG | Eggs per gram |
| ERR | Egg reduction rate |
| EU | European Union |
| FDA | Food & Drug Administration |
| GCP | Good clinical practice |
| Hb | Haemoglobin |
| ICF | Informed consent form |
| ICH | International council for harmonization of technical requirements for pharmaceuticals for human use |
| IEC | Independent ethics committee |
| MDA | Mass drug administration |
| NLME | nonlinear mixed-effects |
| PC | Preventive chemotherapy |
| PHL-IdC | Public Health Laboratory Ivo de Carneri |
| PI | Principal investigator |
| PK | Pharmacokinetics |
| PSAC | Preschool-aged children |
| SAE | Serious adverse event |
| SNSF | Swiss National Science Foundation |
| STH | Soil-transmitted helminths |
| SUSAR | Suspected unexpected serious adverse reaction |
| Swiss TPH | Swiss Tropical and Public Health Institute |
| VAS | Visual analogue scale |
| WHO | World Health Organization |

## IV. Synopsis

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| **Sponsor/Sponsor-Investigator** | Prof. Dr. Jennifer Keiser |
| **Study title** | Efficacy, safety and acceptability of ascending doses of ivermectin in combination with albendazole for *Trichuris trichiura* infections in preschool-aged children: a single-blind randomised controlled dose-ranging trial |
| **Short title** | Ivermectin-albendazole combination for *Trichuris trichiura*–infected children |
| **Study acronym** | Iverped |
| **Protocol version and date** | v1, 08 May 2024 |
| **Trial registration** | Registered on https://www.clinicaltrials.gov/ (NCT06184399) |
| **Clinical phase** | Phase 2 trial |
| **Sample size** | 210 participants |
| **Indication** | *Trichuris trichiura* infection (eggs in stool) |
| **Investigational and reference treatment** | Ivermectin orodispersible mini-tablets (ODTs) co-administered with albendazole<br>Reference: albendazole; ivermectin standard tablets co-administered with albendazole |
| **Study rationale** | To provide evidence on the optimal dose of co-administered ivermectin and albendazole in terms of efficacy, safety and acceptability in preschool-aged children (PSAC; aged 2-5 years) infected with *T. trichiura*. Additionally, to compare the pharmacokinetics of the newly developed ODTs and the standard ivermectin tablets in this age group. |

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| **Study objectives** | Our **primary objective** is to determine the ivermectin dose-response relationship in terms of cure rate (CR) in PSAC (2-5 years) infected with *T. trichiura*, assessed at 14-21 days post-treatment by quadruplicate Kato-Katz microscopy.<br>The **secondary objectives** of the trial are:<br>a) to determine the *T. trichiura* egg reduction rates (ERRs) of treatments;<br>b) to determine the CRs and ERRs of treatments against *Ascaris lumbricoides* and hookworm co-infection;<br>c) to evaluate the safety and tolerability of the treatments;<br>d) to characterize population pharmacokinetics (PK) of ivermectin ODTs compared to standard tablets in *T. trichiura* infected individuals;<br>e) to assess the acceptability of the treatments.<br>The **exploratory objective** of this trial is to assess the diagnostic performance of FECPAKG2. |
| **Study design** | Parallel randomised controlled dose-ranging trial |
| **Study product / intervention** | Administration of a single oral dose of ivermectin ODT (100-400 µg/kg) and albendazole (400 mg) |
| **Comparator(s)** | Albendazole (400 mg); ivermectin standard tablets (200 µg/kg) and albendazole (400 mg) |
| **Key inclusion / Exclusion criteria** | **Inclusion:**<br>• Individuals aged 2-5 years (24-71 months; confirmed by birth certificate or similar document);<br>• having given written informed consent signed by parents/caregivers;<br>• being able and willing to provide two stool samples at baseline and at follow-up assessment (14-21 days);<br>• having at least two out of four Kato-Katz slides positive for *T. trichiura* at baseline;<br>• being able and willing to be examined by a study physician before and after treatment.<br>**Exclusion:** |

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| | • presence or signs of major systemic illness, *e.g.* fever (temporal body temperature of >38.0°C), severe anaemia (haemoglobin level of <70 g/l);<br>• history of severe acute disease or unmanaged, severe chronic disease (*i.e.,* condition is not as therapeutically controlled as necessary);<br>• use of anthelminthic drugs during study period;<br>• known allergy to study medication (*i.e.,* ivermectin or albendazole);<br>• being prescribed or taking concomitantly medication with known contraindications or drug interactions with the study medication;<br>• concurrent participation in other clinical trials. |
| **Primary endpoints** | • *T. trichiura* infection status of participants at 14-21 days post-treatment assessed by quadruplicate Kato-Katz |
| **Secondary endpoints** | • *T. trichiura* infection intensity of participants at 14-21 days post-treatment assessed by quadruplicate Kato-Katz<br>• *A. lumbricoides* and hookworm infection status and intensity of co-infected participants at 14-21 days post-treatment assessed by quadruplicate Kato-Katz<br>• Adverse events (AEs)<br>• Population PK parameters of ivermectin ODTs and standard tablets in *T. trichiura* infected PSAC<br>• Acceptability (including palatability) |
| **Exploratory endpoints** | • Diagnostic characteristics of FECPAKG2 (infection intensity, sensitivity, and specificity) compared to Kato-Katz |
| **Interim analyses** | None |
| **Study duration** | 3 months |
| **Schedule** | 05/2024: of first participant in (planned)<br>07/2024: of last participant out (planned) |
| **Study centres** | *T. trichiura* endemic villages, Wete district, Pemba Island, Tanzania |

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| **Measurements & procedures** | For the initial diagnosis and efficacy assessment at 14-21 days post-treatment, two stool samples will be collected from each participant on two consecutive days. All stool samples will be examined for presence of *T. trichiura*, *A. lumbricoides,* and hookworm eggs with duplicate Kato-Katz thick smears assessed via bright-field microscopy. The medical history of the participants will be assessed with a standardised questionnaire, in addition to a clinical examination carried out by the study physician before treatment. Parents/caregivers will be interviewed before treatment and at three and 24 hours and 14-21 days post-treatment for the occurrence of AEs. Any potential AEs happening between 3 hours and the respective follow-up time points will be monitored by local healthcare workers and medical intervention provided if necessary. Each participant will be asked to provide a finger-prick blood sample for haemoglobin measurement at baseline. At the same time, anthropometric measurements (*i.e.* height, and weight) will be taken for all participants.<br>To determine PK parameters of ivermectin ODTs and standard tablets, a subsample of 12 study participants per relevant treatment arm (ivermectin ODT 200 µg/kg and ivermectin tablet 200 µg/kg) will be asked to provide a maximum of 5 micro blood samples per participant using finger pricks at defined time points between 1 hour and 24 hours.<br>To determine the acceptability of ivermectin ODTs compared to standard tablets, the palatability of each formulation will be rated by children aged 4-5 years using a 100 mm visual analogue scale (VAS). Additionally, participants will complete a short questionnaire right after treatment administration. |
| **Statistical analyses** | An available case analysis (full analysis set according to the intention to treat principles) will be performed, including all participants with primary endpoint data. Additionally, a per-protocol analysis will be conducted. CRs will be calculated as the percentage of egg-positive participants at baseline who become egg-negative after treatment.<br>Geometric and arithmetic mean egg counts will be calculated for the different treatment arms before and after treatment to assess the corresponding ERRs. Bootstrap resampling with 5,000 replicates will be used to calculate 95% confidence intervals (CIs) for ERRs. |

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| | Using the DoseFinding package of the statistical software environment R, $E_{max}$ models will be implemented to predict the dose-response curves based on CRs and ERRs.<br>AEs will be compiled into frequency tables and compared between treatment groups using descriptive summary statistics.<br>With regard to population PK parameters, Cmax and tmax will be observed values, AUC and $t_{1/2}$ will be calculated using nonlinear mixed-effects (NLME) modelling with the WinNonlin software package. In addition, exploratory pharmacometric PK and exposure-response analyses may be performed with the Monolix or NONMEM software package.<br>The VAS score for the palatability will be summarised using descriptive statistics according to formulation. |
| **GCP statement** | This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ICH-GCP E6 (R2) as well as all national legal and regulatory requirements. |
| **Key explanation for the inclusion of children** | This study will involve children aged 2-5 years, since an infection with *T. trichiura* occurs often in children. The main goal of the study is to evaluate for the first time the efficacy and safety of a newly developed child-friendly formulation of ivermectin in this age group. This will allow that preschool aged children can also be included in deworming campaigns with ivermectin-albendazole combination. |
| **Recruitment procedure** | The trial will be conducted on Pemba Island, Tanzania. It will take place in areas with moderate to high *T. trichiura* endemicity (communities with a prevalence of ≥20%) identified from earlier studies and/or based on experience of the local collaborating team. |
| **Coverage of damages** | Winterthur Insurance, Policy No. 4746321;<br>Pemba: National Insurance Cooperation of Tanzania LTD, Policy No. IMIS/GL/P/25/1/2024/771418 |
| **Storage of data and samples for future research aims** | After the study has been completed, all samples will be destroyed. Case report forms and electronic source data will be kept for a minimum of 15 years. |

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| **Conflict of interest in relation to the investigated drugs** | We declare no conflict of interest in relation to the investigated drugs. |

## 2. Background information

Trichuriasis is a parasitic disease caused by nematodes belonging to the group of soil-transmitted helminths (STH). It is estimated that around 400 million people harbour infections with *Trichuris trichiura* globally [1]. As it is the case for all STH infections, trichuriasis is mainly endemic in developing countries in tropical and subtropical regions, with highest burden among rural communities due to its link to poor sanitation [2].

Infection with *T. trichiura* occurs when ingesting embryonated eggs via soil-contaminated hands, drinking water or food. Having reached the small intestine, the eggs hatch realising the larvae. The larvae migrate directly into the cecum where they develop into adult worms and begin to oviposit. Eggs are excreted into the soil via the faeces, thereby closing the life cycle [3].

Acute symptoms of trichuriasis are generally mild or not apparent in infected individuals living in endemic areas [2, 4]. The main disease burden results from chronic infection and repeated re-infection, in which symptoms related to the location of adult worms such as abdominal pain may develop. Long-term infection compromises the life of people by hampering their physical and mental development, limiting their work performance and overall quality of life [4].

The recent World Health Organization (WHO) road map for neglected tropical diseases targets STH infections for near to global elimination as a public health problem by 2030 [5]. One important intervention to achieve this is preventive chemotherapy (PC) [5-7]. The aim of PC is to reduce worm burden and hence morbidity in endemic populations by regular large-scale administration of anthelminthic drugs to high-risk groups, *e.g.* preschool-aged and school-aged children [8, 9]. The frequency of such mass drug administration (MDA) depends on the local infection prevalence [8, 9].

At present, the benzimidazoles albendazole and mebendazole are the most widely used drugs for PC campaigns against STH infections [7, 10]. These drugs are characterized by high cure rates (CRs) against infections with *Ascaris lumbricoides* (>95%) and moderate CRs against hookworm infections (80%). However, at single oral doses suitable for MDA, these drugs have demonstrated unsatisfactory efficacy against *T. trichiura* infections [11, 12].

Therapies combining two or more drugs are widely advocated in different therapeutic areas. The advantages of multifactorial pharmacological treatment include the increase and broadening of efficacy over drugs being administered in monotherapy and the protection against the selection of drug resistance, and hence, a prolongation of the life-span of effective and available drugs [13-15]. In 2017, ivermectin in combination with albendazole for treatment of STH was added to the Essential Medicines List (EML), paving the way to further evaluate the efficacy of this combination treatment among children and communities in a range of epidemiological settings [16]. While evidence on the superiority of ivermectin-albendazole combination compared to single standard treatments against STH infections, including trichuriasis, in school-aged children, adolescents and adults is growing, efficacy of this combination has not yet been assessed in the high-risk population of preschool-aged children (PSAC)

[17, 18]. An important reason for this knowledge gap is that oral ivermectin is not licensed for treatment of individuals with a bodyweight of <15 kg (corresponding to children aged less than ~5 years). Nevertheless, within the past two decades the safety data on individuals weighing <15 kg increased substantially and there are many efforts to develop oral ivermectin for small children suffering from scabies [19].

Another major drawback in the applicability of oral ivermectin in PSAC is the lack of a formulation suitable for administration to small children who may not be able to swallow the standard ivermectin tablets. Tablets offered to young children in a crushed or suspended form are prone to imprecise dosing and come with reduced palatability, and thereby a higher chance to be expelled out of the mouth by the child. Currently, several new orodispersible tablet (ODT) formulations, which are suitable for the hot and humid tropical conditions found in most countries in need, are being developed.

There is a need to explore whether these new ivermectin ODT formulations could reveal a benefit in the treatment of STH infections in PSAC. Based on the data of a study investigating the optimal ivermectin dose in PSAC infected with *T. trichiura* in Côte d'Ivoire, it was suggested to administer higher doses than the standard dose in adults (200 µg/kg) to reach equivalent bioavailability [20, 21]. In this trial, we aim to determine the optimal dose of ivermectin, as a newly developed orodispersible tablet formulation, in combination with albendazole in terms of efficacy and safety in treating *T. trichiura* infections in PSAC on Pemba Island, Tanzania. Furthermore, we re-assess pharmacokinetic (PK) parameters of ivermectin ODTs compared to standard ivermectin tablets. The PK characterization of a drug is essential to understand the response of the human body to a drug and vice versa, especially in populations that physiologically differ from healthy adults. Physiological characteristics like mal- or undernutrition due to intestinal worms, such as *T. trichiura*, can potentially affect the PK of a drug [22, 23]. Age, sex, bodyweight but also the presence of certain enzymes in different populations are important contributors to the PK profile of a drug. Our study will be the first one to provide PK information on a new ivermectin ODT in PSAC with trichuriasis and thus guide optimal drug dosing in this high-risk population. Finally, acceptability (including palatability) of a drug is important to ensure compliance and effectiveness of treatment. Therefore, this study includes the assessment of drug acceptability applying visual analogue scales (VAS).

## 3. Trial objective and purpose

We designed a dose-ranging trial to identify the most appropriate dose of ivermectin in terms of efficacy and safety in treating trichuriasis in individuals aged 2-5 years on Pemba Island, Tanzania. This study will provide further insights on the pharmacokinetics and acceptability of a novel orodispersible formulation as compared to the standard tablets. Our data will pave the way for possible phase 3 follow-up studies and support the development of ivermectin for children aged <6 years and its implementation in control programs.

The **primary objective** is to determine the ivermectin dose-response relationship in terms of CR in *T. trichiura*-infected children aged 2-5 years, assessed at 14-21 days post-treatment by quadruplicate Kato-Katz microscopy.

The **secondary objectives** of the trial are:

a) to determine the *T. trichiura* egg reduction rates (ERRs) of treatments;
b) to determine the CRs and ERRs of treatments against *Ascaris lumbricoides* and hookworm co-infection;
c) to evaluate the safety and tolerability of the treatments.
d) to characterize population PK of ivermectin ODTs compared to standard tablets in *T. trichiura* infected individuals;
e) to assess the acceptability of the treatments.

The **exploratory objective** of this trial is to assess the diagnostic performance of FECPAKG2.

# 4. Methodology

## 4.1 Primary and secondary endpoint

**Primary endpoint:** *T. trichiura* infection status of participants at 14-21 days post-treatment assessed by quadruplicate Kato-Katz.

**Secondary endpoints:**

- *T. trichiura* infection intensity of participants at 14-21 days post-treatment assessed by quadruplicate Kato-Katz;
- *A. lumbricoides* and hookworm infection status and intensity of co-infected participants at 14-21 days post-treatment assessed by quadruplicate Kato-Katz;
- Tolerability of treatments (adverse events (AEs) at three and 24 hours and 14-21 days post-treatment;
- Population PK parameters of ivermectin ODTs and standard tablets in *T. trichiura* infected PSAC;
- Acceptability (including palatability).

**Exploratory endpoints:** Diagnostic characteristics of FECPAKG2 (infection intensity, sensitivity, and specificity) compared to Kato-Katz.

## 4.2 Trial design

A parallel randomised controlled dose-ranging trial will be conducted with six treatment arms (Figure 1). The study includes a baseline screening (day -60 to -1) and clinical baseline assessment (day 0) before treatment and post-treatment assessments for, pharmacokinetics (day 0 to 1), safety (day 0, 1 and 14 to 21) and efficacy (day 14 to 21). It is designed as a dose-ranging trial with 210 participants aged 2-5 years randomised to ivermectin ODT placebo and albendazole (400 mg), ascending doses of ivermectin ODT (100 µg/kg, 200 µg/kg, 300 µg/kg, or 400 µg/kg, respectively) and albendazole (400

mg), or the standard ivermectin tablets (200 µg/kg) and albendazole (400 mg), with an allocation ratio of 1:1:1:1:1:1 (*i.e.*, 35:35:35:35:35:35). This trial will be conducted in communities in the Wete district on Pemba Island with high endemicity as identified in previous studies on *T. trichiura*.

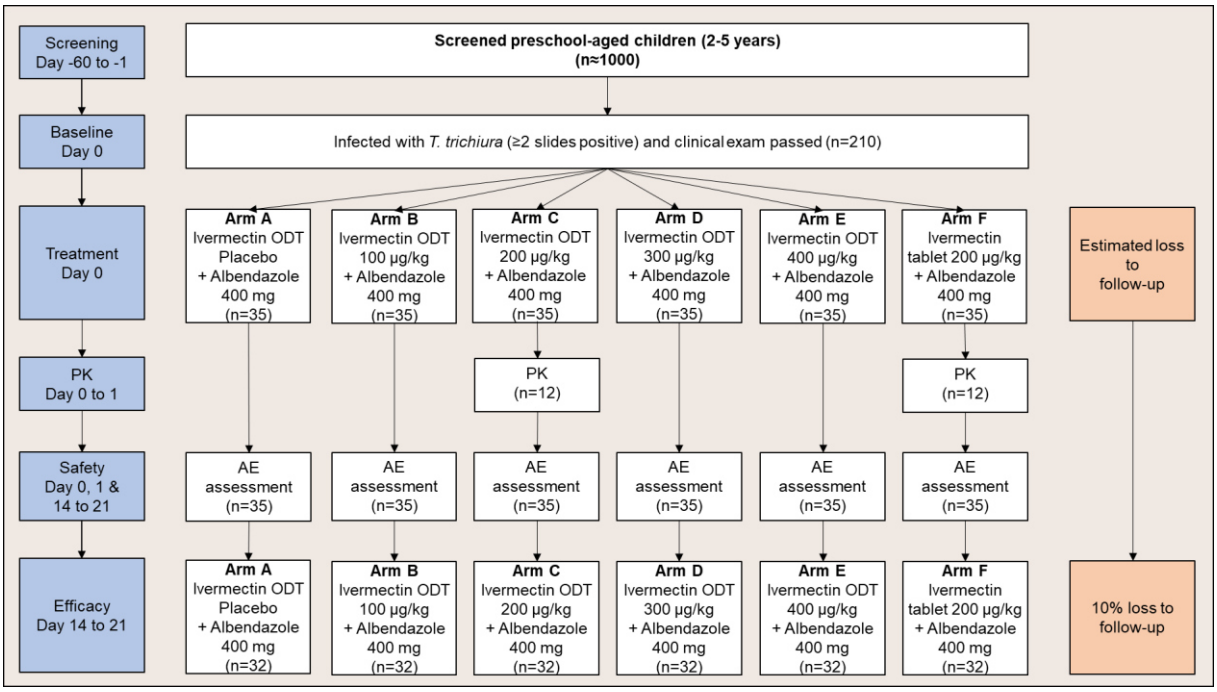


**Figure 1**. Trial design and timeline.

## 4.3 Procedures

### 4.3.1 Diagnosis

At baseline, all participants will be asked to provide two stool samples. From each stool specimen, duplicate Kato-Katz thick smears (41.7 mg each) [24] will be prepared and read under a microscope for eggs of *T. trichiura, A. lumbricoides* and hookworm by experienced technicians. Eggs per gram (EPG) will be assessed by adding up the egg counts from the quadruplicate Kato-Katz thick smears and multiplying this number by a factor of six. For quality control of *T. trichiura* and *A. lumbricoides* egg counts, 10% of slides will be re-read by another laboratory technician. Results are considered correct if the following tolerance margin is not exceeded: (i) No difference in presence/absence of *T. trichiura* and *A. lumbricoides* (ii) egg counts are +/-10 eggs for counts ≤100 eggs or +/-20% for counts >100 eggs (for each species separately). In case discrepancies above the tolerance margin are noted in one or more slides, the respective slides are re-read by the local technicians. The new results are discussed, so that in case of discordant results, slides can be re-evaluated to reach consensus. All microscopically analysed quadruplicate Kato-Katz thick smears will be destroyed after passing the quality control. The same diagnostic approach will be applied at 14-21 days after treatment (see section 4.3.8).

### 4.3.2 FECPAKG2

Research on new diagnostic tools is necessary, since the currently recommended Kato-Katz technique has a low sensitivity for low STH infections and slides with hookworm eggs cannot be re-examined [25-27]. Once moving towards transmission control and STH elimination, an increased sensitivity of the diagnostic method of choice is crucial [28]. Preferably, a diagnostic method that could potentially replace Kato-Katz would be sensitive, specific, fast, simple, cost-effective and re-analysis could be conducted at any time.

The aim of this exploratory objective within this this trial is the comparison of infection intensity, sensitivity, and specificity of the Kato-Katz technique with the novel diagnostic tool FECPAKG2 (Techion). FECPAKG2 is an online, remote location, parasite diagnostic system used in veterinary medicine [29]. An image of the Kato-Katz slide is captured, stored offline on a computer, and can be uploaded onto a cloud once connected to the internet. Subsequently, specialists around the world can analyse the image at any time. Techion's image capture devices are robust, reliable, versatile and cost effective [30]. Baseline quadruplicate Kato-Katz thick smears will be used to take images by FECPAKG2 after the slides have been read by technicians under the microscope.

### 4.3.3 Clinical examination

A clinical examination of the study participants assessing general health, anthropometric parameters including height and weight as well as temperature using a non-contact infrared forehead thermometer (Braun No touch – NTF3000; Braun, Kronberg, Germany) will precede the treatment. Each participant will be asked to provide a finger-prick blood sample to measure haemoglobin (Hb) levels, which will be detected using a HemoCue analyzer (Hb 301 system, Angelholm, Sweden). In case of abnormal values, results from baseline clinical examination may be reported back to parents/caregivers during the trial period. Parents/caregivers of trial participants will be asked about existing clinical symptoms before drug administration using a standardised questionnaire.

### 4.3.4 Treatment of participants

All eligible participants will be treated with the respective treatment regimen according to their treatment arm assigned by randomisation at day 0. Ivermectin tablets (ODT and standard tablets) will be obtained from Liconsa, and an individual number of tablets according to bodyweight and dose will be administered. Albendazole will be the product of GSK (Zentel®) and a single tablet of 400 mg will be administered. Placebo tablets will be purchased from Zentiva Pharma GmbH, Germany.

The tablets will be handed out from four drug containers (placebo, ivermectin ODT, ivermectin standard tablets, and albendazole). According to the randomisation list, each person will receive either:

(i) Placebo (number corresponding to 200 µg per kg bodyweight) plus a single tablet of albendazole
(ii) 100 µg ivermectin ODT per kg bodyweight plus a single tablet of albendazole
(iii) 200 µg ivermectin ODT per kg bodyweight plus a single tablet of albendazole

(iv) 300 µg ivermectin ODT per kg bodyweight plus a single tablet of albendazole
(v) 400 µg ivermectin ODT per kg bodyweight plus a single tablet of albendazole
(vi) 200 µg ivermectin standard tablets per kg bodyweight plus a single tablet of albendazole

All drugs will be administered in the presence of the Principal Investigator (PI) and/or Co-PI, and ingestion confirmed. This will be recorded with the time and date of dosing. Participants will be asked to limit the use of any drugs other than those prescribed by the study medical team for the duration of the study as described in section 5.5. After ingestion of the medication, the participants will be observed for three hours to ensure retention of the drug. Vomiting within one hour post-dosing will require re-dosing. The participants will not be allowed more than one repeated dose. No re-administration will be needed for participants vomiting after one hour. The PI or the Co-PIs are responsible for drug accountability at the study site. Maintaining drug accountability includes careful and systematic study drug storage, handling, dispensing, and documentation of administration. Prior to administration, drugs will be stored at room temperature and protected from light and exposure to moisture in a secure area with limited access at the study site.

To avoid interference of potential on-going control programs against helminthiases with the infection status of the trial participants, communication with local stakeholders will be established to ascertain that trial participants will not undergo MDA treatment. Missed-out rounds of planned MDA against STH infections will be substituted with a free single-dose treatment (albendazole 400 mg) against STH infection after the follow-up assessment, offered by the study team to all community members not participating in the trial in communities screened.

#### 4.3.5 Pharmacokinetic analysis

The PK and exposure-response correlation study will be performed in 24 participants in the two treatment arms receiving either ivermectin ODT 200 µg/kg or ivermectin standard tablets 200 µg/kg (12 per selected treatment arm). Since PK population parameters of ivermectin are available, a sparse sampling approach can be applied to describe the PK profile [31]. Within a sparse sampling approach, instead of describing the PK profile for each participant separately, samples are allocated to different time points and/or individuals within the same treatment. Statistical inferences are performed to characterize the population-based PK profile of a specific treatment arm. This approach allows for a reduced number of samplings per treatment arm and renders a PK characterization well tolerable. To this end, a small drop of blood from the fingertip will be taken for a maximum of 5 finger pricks per participant. The exact time points are 1h, 2h, 4h, 6h, and 24h, covering the relevant time span identified previously [31, 32]. Capillary blood (~60 µl) will be collected by puncture with a finger prick. Two micro-samples (duplicates) will be taken with one finger prick. Each time, the drop of blood (60 µl) will be directly transferred on dried-blood spot cards. The dried cards will be transported to Swiss TPH and stored at room temperature until analysis (< 2 months post-treatment). The quantification of the study

drugs will be performed using the validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method as described elsewhere [32]. Drug concentrations will be calculated by interpolation from a calibration curve with a lower limit of quantification of 1-5 ng/ml. 7% of the sample duplicates will be analysed for quality control, and the measured concentrations will be used to determine between-run and overall precision and accuracy of the analysis.

### 4.3.6 Assessment of acceptability

To better understand the acceptability of ivermectin ODT compared to standard ivermectin tablets in PSAC, the palatability of each formulation (ODT and standard tablets crushed and swallowed with water) will be rated by children aged 4-5 years using a 100 mm VAS incorporating a 5-point pictorial hedonic scale (Figure 2) [33]. This rating will take place within 5 minutes after receiving the treatment. Additionally, participants will complete a short questionnaire directly after treatment administration and the interviewers will observe the participants during medication administration and record any discomfort or difficulties in taking the medication.

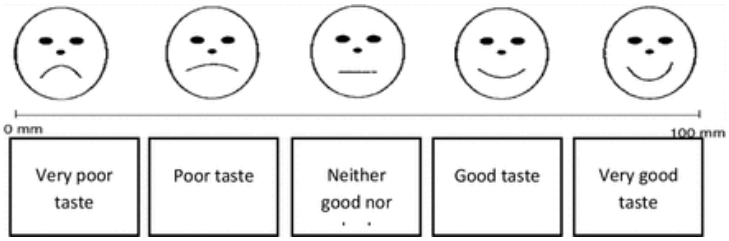


**Figure 2.** 100 mm hedonic visual analogue scale [33].

### 4.3.7 Safety assessment

Participants will be monitored at the site (*i.e.* health centre) for three hours after treatment administration to observe any possible acute AEs (continuous observation) and reassessment will be done at 24 hours post-treatment (follow-up visit). Additionally, interviews will be conducted with parents/caregivers to determine the emergence of clinical symptoms such as headache, abdominal pain, itching, nausea, vomiting and diarrhoea directly before treatment within the scope of baseline assessment. At three and 24 hours and 14-21 days after treatment parents/caregivers will again be interviewed for the assessment of AEs. Symptoms arising within three hours after treatment and the follow-up time points will be monitored by parents/caregivers or local healthcare workers who will report incidences to the study team. Any symptoms will be recorded in the designated case report form (CRF) and immediate action will be undertaken if indicated.

### 4.3.8 Efficacy assessment

The efficacy of the treatment will be determined at 14-21 days post-treatment by collecting another two stool samples, which will be microscopically examined for *T. trichiura, A. lumbricoides* and hookworm eggs using quadruplicate Kato-Katz thick smears (two slides per sample). Quality control will be performed as described for the initial diagnosis (see section 4.3.1). All microscopically analysed quadruplicate Kato-Katz thick smears will be destroyed after passing the quality control.

Participants will be considered cured for an infection if no corresponding eggs are found in the follow-up stool samples. At the end of the study, all participants remaining positive for *T. trichiura* or any co-infection will be treated with the currently best recommended treatment.

### 4.4 Measure to minimise bias

Study participants eligible for treatment will be randomly assigned to one of the six treatment arms using a computer-generated stratified randomisation code. The random allocation sequence with a block size of 6 stratified by two levels of age category (24-47 months and 48-71 months) and two levels of baseline *T. trichiura* infection intensity (light: 1-999 EPG, and moderate or heavy: ≥1000 EPG) will be provided by a statistician. Allocation concealment will be warranted using opaque, sealed envelopes containing the randomisation lists. All treatment arms will be single-blinded (*i.e.* study participants will be blinded) using appearance and texture matching placebos. Only the study pharmacist administering the treatment will be aware of treatment allocation; all trial team members assessing the outcomes will remain uninformed. In the case of accidental unblinding or necessary code breaks, the sponsor will be immediately notified (within 24 hours) and data will be analysed as set forth in section 8.3.

### 4.5 Study duration and duration of participation

The trial will last three months. Baseline screening is scheduled to start two months prior to treatment and follow-up stool sample collection will take place at 14-21 days after treatment, lasting approximately two weeks. Thus, the maximum time for participation will be three months. Schedules of visits are summarised in Table 1.

**Table 1.** Schedule of study visits.

| | **Screening** Day -60 to -1 | **Baseline/Treatment/Safety** Day 0 | | | | | | | **Follow up** Day 14 to 21 |
|---|---|---|---|---|---|---|---|---|---|
| | | 0h | **Randomisation and treatment** | 1h | 2h | 3h | 4h | 6h | 24h | |
| **Informed consent** | X | | | | | | | | | |
| **Diagnosis (stool examination)** | X | | | | | | | | | X |
| **Medical history** | | X | | | | | | | | |
| **Clinical examination** | | X | | | | | | | | |
| **Haemoglobin measurement** | | X | | | | | | | | |
| **PK (microsampling)** | | | | X | X | | X | X | X | |
| **Capturing AEs and SAEs** | | | | | | X | | | X | X |

## 5. Selection of trial participants

## 5.1 Recruitment

The trial will be carried out in children aged 2-5 years in the Wete district, Pemba Island, Tanzania. The trial will be implemented as community-based study in communities with endemicity of *T. trichiura* infection above 20% identified during previous trials. Parents/caregivers of potential participants will be invited to participate in an information session. The research team will explain the purpose and procedures of the study, as well as potential benefits and risks of participation. Attendees will be encouraged to ask questions which will be discussed in an open setting.

Caregivers interested in having their child participate in the study will be invited to complete the informed consenting process by signing the informed consent form (ICF). Participants having a signed ICF will be assessed for eligibility during screening procedures.

## 5.2 Inclusion criteria

1. Aged between 2 and 5 years (24-71 months; confirmed by birth certificate or similar document).
2. Written informed consent signed by parents/caregivers.
3. Agree to comply with study procedures, including provision of two stool samples at the beginning (baseline) and at follow-up assessment 14-21 days after treatment.
4. At least two slides of the quadruplicate Kato-Katz thick smears positive for *T. trichiura*.
5. Willing to be examined by a study physician prior to treatment.

## 5.3 Exclusion criteria

1. Presence or signs of major systemic illness, *e.g.* fever (temporal body temperature ≥ 38°C) or severe anaemia (Hb level <70 g/l according to WHO [34]) upon initial clinical assessment.
2. History of severe acute disease or unmanaged, severe chronic disease (*i.e.,* condition is not as therapeutically controlled as necessary).
3. Use of anthelminthic drugs during study period.
4. Known allergy to study medication (*i.e.* ivermectin, albendazole).
5. Being prescribed or taking concomitantly medication with known contraindication or drug interactions with the study medication.
6. Concurrent participation in other clinical trials.

## 5.4 Criteria for discontinuation of trial

A participant can be discontinued from the study for the following reasons:

1. Withdrawal from the study (this can happen anytime as participation is voluntary and there are no further obligations once a participant withdraws).
2. At the discretion of the PI or Co-PI, if the participant is not compliant to the requirements of the protocol.

Discontinued participants will not be replaced. If, for any reason, a participant is discontinued from the study before the end of treatment evaluations, the AE assessment will still be conducted. Data obtained

prior to the withdrawal will be included in the analysis to ensure the validity of the trial. Data of withdrawn participants are fully anonymised once analysis is complete.

### 5.5 Concomitant medication

All medications taken between one month before treatment and the follow-up assessment at 14-21 days post-treatment must be recorded with indication, dose regimen, date and time of administration.

Medication(s)/treatment(s) permitted during the trial:
- Analgesics and antipyretics are allowed to be given to participants in case of fever, antiemetics to prevent nausea and vomiting and/or antibiotics to prevent or treat bacterial superinfection.

Medication(s)/treatment(s) NOT permitted during the trial:
- No other active drugs against helminths are permitted during the trial. Participants receiving active anthelminthic concomitant medication during the trial will not be discontinued; however, a case-specific assessment will be done at the point of data analysis.

## 6. Safety assessments

### 6.1 Adverse event definitions

The term “adverse event” (AE) is defined as follows:
*Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.*

An AE could therefore include any of the following events, which develop or increase in severity during the course of the study, after administration of the study product:

a. Any unfavourable and unintended signs, symptoms or disease temporally associated with the use of a medicinal product, whether or not considered related to the condition under study and the study product.
b. Any abnormality detected during physical examination.

The medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial will not be defined as AEs, but considered as baseline medical conditions. For the purpose of this trial, disease progression and relapse will be considered as failure of prescribed treatment or failure of treatment administration, not as an AE.
The observation time for AEs starts when the treatment is initiated until the end of the study.
These data will be recorded on the appropriate CRF sections, regardless of whether they are thought to be associated with the study or the drug under investigation. Associated with the use of the drug means

that there is a reasonable possibility that the event may have been caused by the drug (see also relatedness definitions below).

### 6.1.1 Severity grading

Adverse signs or symptoms will be graded by the physician or nurse of the trial as mild, moderate, severe or life threatening according to the following definitions:

| Grade | Definition |
|---|---|
| 1 | Mild: the participant is aware of the event or symptom, but the event or symptom is easily tolerated. |
| 2 | Moderate: the participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity. |
| 3 | Severe: significant impairment of functioning: the participant is unable to carry out his or her usual activities. |
| 4 | Life-threatening or disabling |
| 5 | Death related to AEs |

### 6.1.2 Relatedness

Relatedness will be assessed as defined below based on the temporal relationship between the AE and the treatment, known side effects of treatment, medical history, concomitant medication, course of the underlying disease and trial procedures.

Possibly related: an AE, which can medically (pharmacologically/clinically) be attributed to the study treatment.

Unrelated: an AE, which is not reasonably related to the study treatment. A reasonable alternative explanation must be available.

An AE that is determined to be related to the administration of a study product is referred to as an "adverse drug reaction".

### 6.1.3 Expectedness

Expected adverse drug reaction: Any AE possibly related to the administration of ivermectin, albendazole or ivermectin-albendazole combination reported in the literature or on the drug package leaflets, if available, and listed in the consent form.

Unexpected adverse drug reaction: Any AE possibly related to the study drug administration, the nature, frequency, specificity or severity of which is unanticipated and not consistent with the available risk information described for these drugs.

### 6.1.4 Serious adverse events

According to the ICH "Clinical Safety Data Management: Definitions and standards for expedited Reporting E2A" [35], a serious adverse event (SAE) includes any event (experience) or reaction in any untoward medical occurrence that at any dose:

1. results in death;
2. is life-threatening, meaning, the participant was, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, *i.e.* it does not include a reaction that, had it occurred in a more serious form, might have caused death;
3. results in persistent or significant disability/incapacity, *i.e.* the event causes a substantial disruption of a person's ability to conduct normal life functions;
4. requires inpatient hospitalization or prolongation of existing hospitalization;
5. creates a congenital anomaly or birth defect (not relevant for this study);
6. is an important medical event, based upon appropriate medical judgement, that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes defining serious.

A "severe" AE does not necessarily meet the criteria for a "serious" AE. SAEs are reported from treatment until the end of the study.

SAEs that are still ongoing at the end of the study period will be followed up to determine the final outcome.

The causality of any SAE that occurs after the study period and its possible relatedness to the study treatment or study participation will also be assessed by investigators as described in section 6.1.2.

### 6.1.5 Suspected unexpected serious adverse reactions

A suspected unexpected serious adverse reaction (SUSAR) is an unexpected adverse drug reaction, which also meets the definition of SAE.

## 6.2 Methods of recording and assessing adverse events

Few AEs have been reported following ivermectin, albendazole, or ivermectin-albendazole co-administration in STH infected individuals. The most common AEs were abdominal cramps, headache, fatigue, nausea, diarrhoea, fever, and vertigo. Such symptoms can, however, also result from the infection itself. Such side effects may be more frequent and/or serious in patients with a heavy worm burden.

The observation time for AEs starts when the treatment is initiated. Participants will be observed for at least three hours following treatment for any acute AE and reassessment will be done at 24 hours and 14-21 days post-treatment. If there is any abnormal finding, the local study physician will perform a full clinical examination and findings will be recorded. An emergency kit will be available on site to treat any medical conditions that warrant urgent medical intervention. Participants will also be interviewed

at three and 24 hours as well as at 14-21 days after treatment about the occurrence of AEs. Any potential AEs happening between three hours post-treatment and the further follow-up time points (24 hours and 14-21 days) will be monitored and managed with the help of the locally based medical team (including specifically trained community health workers, nurses and medical doctors). Medical intervention will be provided if necessary.

Information on all AEs (incidence, intensity, seriousness and causality) will be entered immediately in the appropriate AE module of the CRF. For all AEs, sufficient information will be pursued and/or obtained so as to permit i) an adequate determination of the outcome of the event (*i.e.* whether the event should be classified as a SAE); and; ii) an assessment of the casual relationship between the AE and the study treatments. Intensity of AE will be judged by the study physician, following guidelines by the European Medicines Agency (Note for Guidance on Clinical Safety Data Management).

All SAEs, unexpected adverse drug reactions or SUSARs must be reported as described in Section 6.3.

## 6.3 Reporting of serious adverse events

Any study-related unanticipated problem posing risk of harm to participants or others (including all unexpected adverse drug reactions), and any type of SAE will be immediately (within a maximum of 24 hours after becoming aware of the event) notified to the study sponsor-investigator and Co-PIs:

**Prof. Dr. Jennifer Keiser (Sponsor-Investigator/PI)**
Swiss Tropical and Public Health Institute
Kreuzstrasse 2, 4123 Allschwil, Switzerland
Tel.: +41 61 284 82 18
Fax: +41 61 284 81 05
E-mail: jennifer.keiser@swisstph.ch

**Mr. Said Mohammed Ali (Co-PI)**
Public Health Laboratory Ivo de Carneri
P.O. Box 122 Wawi, Chake Chake, Pemba, Tanzania
Tel.: +255 24 245 20 03
E-mail: saidmali2003@yahoo.com

Within the following 48 hours, the local co-investigator must provide further information on the SAE or the unanticipated problem in the form of a written narrative to the study sponsor-investigator. This should include a copy of a completed SAE form, and any other diagnostic information that will assist the understanding of the event. In exceptional circumstances, a SAE may be reported by telephone. In these cases, a written report must be sent immediately thereafter by fax or e-mail. Names, addresses and telephone for SAE reporting will be included in the trial-specific SAE form. Relevant pages from the CRF may be provided in parallel (*e.g.*, medical history, concomitant medications).

### 6.4 Safety reporting to Health Authorities, Ethics Committees and other third parties

The sponsor-investigator will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations. Additionally, this information will be provided to the responsible ethics committees in Switzerland and Zanzibar according to national rules. Fatal or life-threatening SAEs or SUSARs will be reported within 24 hours followed by a complete report within 7 additional calendar days. Other SAEs and SUSARs that are not fatal or life-threatening will be filed as soon as possible but no later than 14 days after first knowledge by the sponsor-investigator. SAEs involving ivermectin ODTs will be reported to the manufacturer.

### 6.5 Rescue medication strategy

In case an adverse event requires medical intervention, this will be performed by the study physician and in accordance with local medical guidelines. Given the most common adverse events (headache, abdominal pain, itching, nausea, vomiting and diarrhoea), analgesics and antipyretics (*e.g.* paracetamol) are allowed to be given to participants in case of pain or fever, antiemetics (*e.g.* dimenhydrinate) to prevent nausea and vomiting and/or antibiotics to prevent or treat bacterial superinfection. In addition, electrolyte replacement solution in case of severe vomiting and diarrhoea, immunosuppressants (*e.g.* dexamethasone) in case of allergies or immune system over-reaction (*e.g.* due to a high amount of worms being expulsed) or an adsorptive antidote (*e.g.* activated charcoal) may be administered.
At the end of the study, all participants remaining positive for *T. trichiura* or any co-infection will be treated with the currently best recommended treatment.

## 7. Data management and data quality control

The investigators are responsible for an adequate data quality. Prior to the initiation of the study, a short investigator's meeting will be held between investigators of Swiss TPH and PHL-IdC. This meeting will include a detailed discussion of the protocol, performance of study procedures (standard operating procedures from previous studies available on site), CRF completion, specimen collection and diagnostic methods.

### 7.1 Source data

Source data are comprised of clinical findings and observations as well as laboratory data maintained and compiled at the study site. Source data are contained in hardcopy source documents and are allowed to be accessed by local authorities. Source data will be directly entered in the following documents:

1. CRF: Primary data collection instrument for the study. It holds records of all clinical and physical examination data, treatment information and AEs. For every participant enrolled in the clinical trial a corresponding CRF exists. All data requested on the CRF must be recorded, and investigators will review and approve each CRF for completion.
2. Census: Holds name, age and sex of each potential participant.

3. Laboratory parasitology sheets: Record of the *T. trichiura, A. lumbricoides* and hookworm egg counts at all sample collection time points.
4. PK: Time records of PK sample collection.

## 7.2 Data collection and documentation

Data collected and produced within this trial will fall into one of the following categories:

a) Egg counts of *T. trichiura*, *A. lumbricoides* and hookworm derived from quadruplicate Kato-Katz microscopy performed at baseline as well as at 14-21 days post-treatment.
b) Anthropometric and clinical characteristics of the trial participants collected using the study's CRF such as weight, height, blood pressure, temperature, overall health status and any abnormal medical condition or chronic disease.
c) Finger prick blood samples for haemoglobin measurement and PK analysis.
d) Collection date and time of each PK sample.
e) Measured concentrations analysed from finger prick blood samples and subsequently derived PK parameters.

All data categories will be recorded paper-based (primary data source), *e.g.* on the CRF, and double-entered into the electronic data collection software REDCap (Vanderbilt University, US) using tablets. In this case, the paper-based data will represent the primary data source. All entries will be printed in blue ink and all corrections must be documented with date and initials of the respective team member. Double-entered data will be compared using the REDCap internal 'Data Comparison Tool' and any discrepancies will be reviewed against the hardcopies of the CRF and corrected accordingly. All data files in REDCap will be merged into a master file and saved as .xlsx and/or .csv file. Data analysis will be conducted with pseudonymised data and reporting of findings will be fully anonymised.

## 7.3 Ethical, legal and security issues

Information about study participants will be kept confidential and managed accordingly. Screened participants will be listed in a confidential "participant screening log" and attributed a unique participant ID (PID). In case of enrolment, participants will be listed in a confidential "participant enrolment log" utilizing the same PID. The PID will be linked with the participant's identity on a separate file (participant identification list), filed in a secured place at PHL-IdC. This document will constitute the only source to decode the pseudonymised data and will only be accessible to investigators. Personal data will be coded for data analysis. No names will be published at any time, and published reports will not allow for identification of single participants. Confidentiality will be ensured throughout the entire research project. All databases will be password secured. None of the investigators declare to have any conflicts of interest.

### 7.4 Data storage and preservation

All samples containing biological material will be destroyed after completion of the study. Paper-based and electronic source data and related material will be preserved for a minimum of 15 years to enable understanding of the study procedures, which allows the work to be assessed retrospectively and repeated if necessary. The study site (PHL-IdC) will retain the original hardcopy source documents such as CRFs to ensure that local collaborators can provide access to these documents to a monitor, auditor, or regulatory agency. Essential infrastructure such as a locked room for safe storage of hardcopy data will be made available. Electronic copies of source documents will be transferred to Swiss TPH, Allschwil, Switzerland, for storage on secured network drives with restricted access for study personnel only. The primary storage of electronic data will be within REDCap on the Swiss TPH shared server and strictly confidential by password protection. The entire REDCap project (including all data) will be backed up regularly, *e.g.* weekly. Secondary data storage will be on personal, password-protected laptops of the PI and Co-PIs, and on a flash drive kept by Co-PIs at the study site.

### 7.5 Study documents: translations – reference language

- The protocol master document will be in English, all further language versions (*e.g.* Kiswahili) are translated thereof.
- The ICF master document will be in English, all further language versions (*e.g.* Kiswahili) are translated thereof.
- The CRF master document will be in English, all further language versions (*e.g.* Kiswahili) are translated thereof.

## 8. Statistics

### 8.1 Definition of primary endpoint

*T. trichiura* infection status 14-21 days post-treatment assessed by quadruplicate Kato-Katz is the primary endpoint in our study.

### 8.2 Justification of number of trial participants

The main aim of this study is to elucidate the nature of the dose-response relationship. A series of simulations was carried out to determine the required sample size. We assumed different sets of true CRs ranging from very optimistic (10%, 45%, 54%, 58% and 60%) to very pessimistic (15%, 30%, 33%, 34% and 35%) for 0, 100, 200, 300 and 400 µg/kg, respectively. Assuming a loss to follow-up of 10%, we estimated that enrolling 35 participants per arm will be sufficient to predict the dose-response curve with a precision (defined as median distance between prediction and confidence band) of about 10 %-points in the relevant dose range from 100 µg/kg to 400 µg/kg. Additionally, 35 individuals will be included for the standard tablet arm. In total, we anticipate to recruit 210 participants.

The suggested sample size of a maximum 5 PK samples from 24 participants (12 per concerned study arm) is sufficiently high to determine the population PK parameters with a sparse sampling scheme.

## 8.3 Description of statistical methods

The primary analysis will use the full analysis set (available case population) according to the intention-to-treat principles defined as all randomised participants who provide any follow-up data. Only randomised participants not providing follow-up data as well as participants who were negative at baseline and erroneously randomised will be excluded from the analysis. In addition, a per-protocol analysis will be conducted. Eligibility for analysis sets will be determined before unblinding. CRs will be calculated as the percentage of egg-positive participants at baseline who become egg-negative after treatment.

EPG will be assessed by adding up the egg counts from the quadruplicate Kato-Katz thick smears and multiplying this number by a factor of six. Geometric and arithmetic mean egg counts will be calculated for the different treatment arms before and after treatment to assess the corresponding ERRs (see formula).

$$ERR = 1 - \frac{\frac{1}{n}\, e^{\sum \log(EPG_{follow-up} + 1)} - 1}{\frac{1}{n}\, e^{\sum \log(EPG_{baseline} + 1)} - 1}$$

Bootstrap resampling method with 5,000 replicates will be used to calculate 95% confidence intervals (CIs) for ERR point estimates. Using the DoseFinding package of the statistical software environment R, hyperbolic $E_{max}$ models will be implemented to predict the curves of the dose-response in terms of CRs and ERRs.

Previous similar trials have shown that the proportion of participants lost to follow-up is usually far below 10%, therefore, no imputation of missing data will be performed. Infection status and egg counts of participants with incomplete data at follow-up (*i.e.* only one stool sample available at follow-up) will be estimated based on the available data. This means a participant is considered infected if any sample is positive and EPGs will be calculated as mean egg count of the available sample multiplied by 12.

The safety analysis set will include all treated participants. AEs will be evaluated descriptively focusing on the proportion of participants reporting symptoms before and after treatment in each arm.

Previously established nonlinear mixed-effects (NLME) models will be used to compare and determine PK parameters [21]. Concentrations are measured with a validated LC-MS/MS method [32]. Using NLME, the following key PK parameters will be calculated:

- $C_{max}$ maximal plasma concentration
- $t_{max}$ time to reach $C_{max}$

- AUC area under the curve, from 0 to 24 h and 0 to inf.
- $t_{1/2}$ elimination half-life

$C_{max}$ and $t_{max}$ will be observed values derived from the plasma concentration-time profile. Total drug exposure (AUC) and $t_{1/2}$ will be calculated with the WinNonlin software package using compartmental analysis. The elimination half-life will be estimated by the equation: $t_{1/2} = \ln 2/\lambda$, where $\lambda$ (the elimination rate constant) will be determined by performing a regression of the natural logarithm of the concentration values during the elimination period. Primary PK parameters including absorption rate ($k_a$), volume of distribution (V), and clearance (CL) will be estimated utilizing NLME modelling. In addition, exploratory pharmacometric PK and exposure-response analyses may be performed with the Monolix or NONMEM software package.

The VAS score for the palatability will be summarised using descriptive statistics according to formulation (ivermectin ODT, and ivermectin standard tablets crushed and swallowed with water). Each of the arms receiving the new formulation (arm A, B, C, D and E) will be tested against the current formulation (Arm F).

# 9. Duties of the investigator

## 9.1 Investigator's confirmation

This trial will be conducted in accordance with the protocol, International Conference on Harmonisation Good Clinical Practice E6 (R2) (ICH-GCP) and the current version of the Helsinki Declaration.[36, 37]
All protocol modifications must be documented in writing. A protocol amendment can be initiated by either the Sponsor-Investigator/PI or any Co-PI. The Investigator will provide the reasons for the proposed amendment in writing and will discuss with the Sponsor-Investigator/PI and Co-PIs. Any protocol amendment must be approved and signed by the Sponsor-Investigator/PI and must be submitted to the appropriate Independent Ethics Committee (IEC) for information and approval, in accordance with local requirements, and to regulatory agencies if required. Approval by IEC must be received before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial participants, or when the change involves only logistical or administrative aspects of the trial, *e.g.* change of telephone number(s).

## 9.2 Damage coverage

A general liability insurance of the Swiss TPH is in place (Winterthur Insurance, Policy No. 4746321) and a participant liability insurance has been issued in Pemba, Tanzania (National Insurance Cooperation of Tanzania LTD, Policy No. IMIS/GL/P/25/1/2024/771418).

### 9.3 Project management

The trial team will include the PI (Prof. Jennifer Keiser), three Co-PIs (Said Mohammed Ali, Viviane Sprecher, Annina Schnoz), a study physician (Dr. Ibrahim Said Mohammed), a study pharmacist (Viviane Sprecher), and a statistician (Dr. Jan Hattendorf), as well as a local medical team and several laboratory technicians. The PI and Co-PIs will be responsible for staff management, communication with the collaborative group, recruitment monitoring, data management, safety reporting, analysis, report writing and dissemination of the trial results. The Co-PIs are responsible for supervision of the lab and field technicians, staff management, participant recruitment and enrolment monitoring, supply of the material, contact to the local authorities and participating communities.

The study site (PHL-IdC) has more than 20 years of research experience with a special focus on neglected tropical diseases, including trichuriasis, and owns well-established diagnostic laboratories in parasitology and other infectious disease fields, run by trained and experienced technicians.

Infrastructure as required for the study needs will be installed as necessary before study launch. The investigator team is responsible for ensuring that the protocol is strictly followed. No changes should be made without the agreement of the PI and the Co-PIs, except when necessary to eliminate an apparent immediate hazard or danger to a study participant. All investigators will work according to the protocol and GCP. All investigators may take any steps judged necessary to protect the safety of the participants, whether specified in the protocol or not. Any such steps must be documented. During the treatment, the records are maintained by the responsible Co-PI. All entries have to be made clearly readable with a pen. All investigators must be thoroughly familiar with the properties, effects and safety of the investigational pharmaceutical product.

## 10. Ethical considerations

### 10.1 Independent Ethics Committee (IEC)

The study will be submitted for approval by the institutional research commission of Swiss TPH and the ethical committees of Switzerland and Zanzibar. The study will be undertaken in accordance with the Declaration of Helsinki and ICH-GCP.

### 10.2 Evaluation of the risk-benefit ratio

Ivermectin and albendazole are well-known drugs and have little and mainly mild AEs as described to date (headache, abdominal pain etc.). Both drugs are approved for and widely used in mass treatment programs against nematode infections. Albendazole is approved in children aged ≥1 year and ivermectin has been tested for trichuriasis in PSAC.[20] All PSAC enrolled in the study will benefit from a clinical examination and a treatment against STH infections. All participants remaining positive for *T. trichiura* or any co-infection will be treated with the currently best recommended treatment.

### 10.3 Participant information and consent

All parents or caregivers of eligible participants will be asked to sign a written informed consent form. In case the parent/caregiver is illiterate, an impartial witness that can read and write has to sign the consent and the illiterate person has to give a thumb print. Parents or caregivers will have sufficient time for reflection of their child's participation.

Information sessions in the respective communities will be conducted to explain to caregivers and potential participants the purpose and procedures of the study. Informed consent forms are orally explained in local language of the parents/caregivers if necessary to ensure comprehension. Participation is voluntary and individuals have the right to withdraw from the study at any given point in time with no further obligations. Participation itself will not be awarded with compensation.

### 10.4 Participants requiring particular protection

Our study will include PSAC, since this population group is at high risk of *T. trichiura* infection. Our trial will produce more evidence for the use of ivermectin for trichuriasis in children and the whole community.

Throughout the entire study, from the preparation phase to the dissemination of results, community representatives (*e.g.* health centre staff) will be consulted to ensure any concerns regarding the study can be tackled in an anonymous and timely manner and the study addresses the community's needs as far as possible.

## 11. Quality control and quality assurance

### 11.1 Monitoring and auditing

We will work with a locally based external monitor. The monitor will conduct site visits to the investigational facilities with the purpose of monitoring the study. Details will be described in a separate monitoring plan. The investigators will grant access to study documentation, laboratory facilities, and the clinical supplies dispensing and storage area. Monitoring observations and findings will be documented and communicated to appropriate study personnel and management. A corrective and preventive action plan will be requested and documented in response to any significant deviation. No sponsor-initiated audits are foreseen, but audits and inspections may be conducted by the local regulatory authorities or ethics committees. The investigators agree to allow inspectors from regulatory agencies to review records and assist the inspectors in their duties, if requested.

### 11.2 Data and safety monitoring board (WHO) / data monitoring committee (EU/FDA)

In our study, we work with well-known drugs in a small sample size and using a single dose treatment. Nevertheless, the project advisors, Dr Said Abdallah Jongo, physician and senior clinical research scientist at the Ifakara Health Institute (IHI) in Bagamoyo, Tanzania, and Prof Dr Piero Olliaro,

infectious disease physician and professor of infectious diseases associated with poverty at Oxford University, United Kingdom, will serve as independent data and safety monitoring board, they will be informed regularly and the findings discussed. This means they have the responsibility to convene, evaluate the study data and give their advice regarding the continuation or stopping of the study before the treatment, at the end of the study and in case of an important safety event.

## 12. Funding

Funding for this trial is provided by the Swiss National Science Foundation (SNSF). This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results for publication.

## 13. Dissemination of results and publication

The final results of this study will be published in a peer-reviewed scientific journal and presented at scientific conferences. SNSF will be acknowledged as study funder. All results from this investigation are considered confidential and shall not be made available to any third party by any member of the investigating team before publication. A summary of study findings may be shared with local health authorities prior to publication. After publication, study results will be made available to study participants.

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# 15. Appendix

## 15.1 Visual Analogue Scales for palatability

1. Did the drug have a taste?

No taste ——————————————— Very strong taste

|__|__|.|__| cm

2. Was the drug bitter?

Not bitter ——————————————— Very bitter

|__|__|.|__| cm

3. Was the drug sweet?

Not sweet ——————————————— Very sweet

|__|__|.|__| cm

4. Did you like the taste of the drug?

Very unpleasant ——————————————— Very pleasant

|__|__|.|__| cm