Study protocol (amended)

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26.08.2019

Study Protocol

Efficacy and safety of a new chewable tablet of mebendazole *versus* the swallowable, standard tablet of mebendazole against hookworm infections in children on Pemba Island, Tanzania: a randomized controlled trial

Protocol Number	4		
Version Number	4.01	**Document Date**	26.08.2019
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Principal Investigator	Prof. Dr. Jennifer Keiser, Swiss Tropical and Public Health Institute, Tel.: +41 61 284-8218 Fax: +41 61 284-8105 E-mail: jennifer.keiser@swisstph.ch		
Study site	Wawi, Mvumoni, Bwagamoyo, Piki ***and Mzambarauni*** schools, Pemba, Tanzania and Public Health Laboratory Ivo de Carneri, Pemba, Tanzania		
Funding Agency	Swiss National Science Foundation (SNF)		

1. General information

1.1. List of investigators and other persons involved

Title	Names	Institution	Position	Function in trial
Prof. Dr.	Jennifer Keiser	Swiss Tropical and Public Health Institute (Swiss TPH)	Unit head	Principal Investigator
MSc	Marta Palmeirim	Swiss TPH	PhD-student	Co-PI
MSc	Said Ali	Public Health Laboratory Ivo de Carneri (PHL-IdC) Foundation	CEO	Co-PI
PhD	Shaali Ame	PHL-IdC Foundation	Head laboratory Services	Co-PI
Dr.	Jan Hattendorf	Swiss TPH	Project leader	Statistician

1.2. Signatures

Trial statistician

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Title	Dr.	
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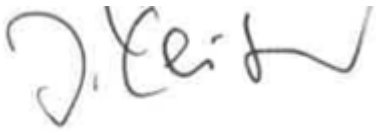
Sponsor and Principal investigator (PI)

Signature		**Date of Signature** 26.08.2019
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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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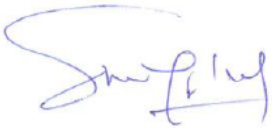
Signature		**Date de Signature** 26.08.2019
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1.3. Abbreviations

AE: adverse event

CI: confidence interval

Co-PI: co-principal investigator

CR: cure rate

CRF: case report form

EPG: egg per gram

ERR: egg reduction rate

GCP: Good Clinical Practice

Hb: haemoglobin

ICH: International Council for Harmonisation

IEC: independent ethics committee

PHL-IdC: Public Health Laboratory Ivo de Carneri

PI: Principal Investigator

SAE: serious adverse event

Swiss TPH: Swiss Tropical and Public Health Institute

STH: soil-transmitted helminths

WHO: World Health Organization

1.4. Synopsis

Study title	Efficacy and safety of a new chewable tablet of mebendazole *versus* the swallowable, standard mebendazole tablet against hookworm infections in children: a randomized controlled trial
Short title	Efficacy of chewable and swallowable MEB tablets
Protocol number, version and date	V4.01, 26.08.2019
Trial registration	Will be registered on http://clinicaltrials.gov/
Study type	Phase 2 trial
Sample size	400
Indication	Hookworm infection
Investigational product and reference treatment	Mebendazole
Study rationale	To provide evidence on the safety and efficacy of a chewable tablet of mebendazole compared to the standard tablet in preschool- and school-aged children infected with hookworm.
Study objectives	To compare the efficacy and safety of two formulations of mebendazole: (i) single dose of 500 mg chewable tablet, and (ii) single dose of 500 mg standard swallowable tablet of mebendazole in participants aged 3-12, inclusive, infected with hookworm. The **primary objective** is to comparatively assess the efficacy in terms of egg reduction rates (ERRs) against hookworm infections using the duplicate Kato-Katz thick smear method on two stool samples among preschool- and school-aged children 14-21 days after the following oral treatment regimens: • 500 mg swallowable tablet of mebendazole • 500 mg chewable tablet of mebendazole

	The **secondary objectives** of the trial are: • To evaluate the safety and tolerability of the two formulations • To evaluate the cure rates (CRs) of the two formulations against hookworm • To determine the CRs and ERRs against *Ascaris lumbricoides* and *Trichuris trichiura* • To investigate the acceptability and age-appropriateness of both formulation when administered to children between 3 and 12 years of age The **exploratory objectives** of this study are: • To assess how well caregivers understand the clinical trials aim, procedures, their rights, risks and potential benefits • To compare the effect of different methods of providing information on their understanding of the clinical trial
Study design	Randomized controlled, open-label, parallel-group, superiority trial (outcome assessors are blinded).
Study product / intervention	Administration of a single oral dose of a 500 mg chewable tablet of mebendazole
Comparator(s)	500 mg swallowable tablet of mebendazole
Key inclusion / exclusion criteria	**Inclusion:** preschool- and school-aged children (3-12 years) with hookworm with at least two slides of quadruplicate Kato-Katz thick smears positive and infection intensities of at least ***50*** eggs per gram of stool (EPG), with written informed consent signed by the caregiver, able and willing to by examined by a study physician before treatment and to provide two stool samples at baseline. **Exclusion:** pregnant, any abnormal conditions or history of major systemic or chronic illnesses, severely anaemic (Hb < 80 g/l), received anthelminthic treatment or metronidazole within the past four weeks, or is attending any other clinical trial during this

	study.
Primary endpoints	ERRs on hookworm, assessed 14-21 days post treatment
Secondary endpoints	CRs against hookworm, assessed 14-21 days post treatment CRs and ERRs against *A. lumbricoides* and *T. trichiura* Safety, assessed 14-21 days post treatment Acceptability and age-appropriateness of the tablets, assessed during treatment
Exploratory endpoints	Caregivers understanding of the clinical trial in general and by caregiver group, assessed during the informed consenting procedure
Interim analyses	None
Study duration	12 weeks total; up to 10 weeks per participant
Schedule	02/2019 of first-participant in (planned) 05/2019 of last-participant out (planned)
Study site	Wawi, Mvumoni, Bwagamoyo, Piki ***and Mzambarauni*** schools, Pemba, Tanzania
Measurements & procedures	A first stool sample will be collected and if the participant is found positive for hookworm a second stool sample will be requested, if possible the next day. The medical history of the participating individuals will be assessed with a standardized questionnaire contained in the case report form, in addition to a clinical and physical examination carried out by the study physician before treatment. This examination also includes pricking subjects' fingers to measure haemoglobin (Hb) levels and, in the case of female participants aged ≥ 10 years, a urine pregnancy test. Randomization of participants into the two treatment arms will be stratified according to intensity of infection. Participants will be interviewed before treatment for clinical symptoms and 3, and 24 hours after treatment to assess occurrence of adverse events (AEs). The efficacy of the treatment will be determined 14-21 days post-treatment by

	collecting another two stool samples. All stool samples will be examined with duplicated Kato-Katz thick smears for hookworm, *A. lumbricoides* and *T. trichiura* eggs. During treatment, a sheet will be filled out for each participant to record his/her behaviour during the process of swallowing the tablet. School-aged children will be asked a few questions about their receptivity and the adequacy of the formulation of mebendazole they received, immediately after treatment.
Statistical analyses	The primary analysis will use the full analysis set (available case population) according to the intention to treat principle defined as all randomized subjects which provide any follow-up data. Only subjects which were negative at baseline and erroneously randomized will be excluded from the analysis. Because palatability and ease of swallowing are critical attributes in children; therefore, a per-protocol analysis will be conducted additionally to disentangle drug efficacy from adherence effects. Geometric 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 and the difference between the two ERRs. Differences in CRs will be assessed using unadjusted logistic regressions. In a subsequent analysis an adjusted logistic regression (adjustment for age, sex, weight and strata) will be performed.
GCP statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ICH-GCP E6 as well as all national legal and regulatory requirements.
Key explanation for the inclusion of children	This study will be carried out in children since infection with hookworm and other soil-transmitted helminths occurs most often in this age group and they will be the population group treated with the new formulation.
Recruitment procedure	This school-based trial will be carried out in ***five*** primary schools with kindergarten (Wawi, Mvumoni, Bwagamoyo, Piki ***and***

	Mzambarauni) on Pemba Island, Tanzania.
Coverage of damages	Winterthur Police Nr. 4746321, National Insurance Cooperation of Tanzania LTD, GTA No: 00062.
Storage of data and samples for future research aims	After the study has been completed all samples will be destroyed and the trial master file will be kept for a minimum of 15 years.
Conflict of interest in relation to the investigated drugs	We declare no conflict of interest in relation to the investigated drugs.

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2. Background information

Soil-transmitted helminthiases are caused by one of the three soil-transmitted helminths (STH), *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm (*Ancylostoma duodenale* and *Necator americanus*). Currently, STH still infect about two billion people worldwide, mostly in tropical and subtropical regions [1]. The global burden of STH infections reached over three million disability-adjusted life years in 2016 [2]. Children living in less developed settings, with crowded living conditions, inadequate sanitation and the lack of access to clean water, harbour the most intense infections [3-6]. These diseases can cause considerable burden including dietary deficiencies, anaemia, physical and cognitive retardation in children and reduction in work performance in adulthood [4, 7-10]. Currently, the main strategy to control STH infections is preventive chemotherapy which consists on the regular administration of either mebendazole (500 mg) or albendazole (400 mg) to children living in regions were these parasites are highly prevalent (WHO 2017). Preventive chemotherapy is promoted by the World Health Organization (WHO), due to its simple implementation and strong impact on morbidity by decreasing worm burden. WHO aims at reducing the prevalence of moderate and heavy STH infections in preschool and school-aged children to below 1% by 2020 [11]. However, there is a lack of appropriate paediatric formulations against soil-transmitted helminths; the mebendazole tablets currently used in mass drug administration programmes are solid (swallowable), which may make them inappropriate for younger age groups to swallow.

The European Medicines Agency recommends swallowable tablets for children aged 6 years or older [12] and the WHO recommends only administering chewable tablets to children aged 5 or younger [13]. Indeed, in the UK, children aged 6 years and older are willing to take tablets of any size (Ranmal et al 2016). However, children as young as 3 years old have been found to easily swallow conventional tablets [14-16] and children above 6 years of age have reported difficulties [17]. A survey in Nigeria found that caregivers prefer liquid formulations because they are sweet and do not require further preparation (Orubu et al 2017). However, solid tablets have significant advantages: they have a lower risk of incorrect administration (Walsh et al 2011) and are easily stored, transported and distributed (WHO 2012). In low-resource settings, as are most of those requiring preventive chemotherapy, the ease of storage, transport and distribution of the drugs is particularly important. Thus, ideally, a formulation which could be transported and stored in a solid form but administered in a semi-solid or liquid form could be a solution for young children.

The WHO's call for a more child-friendly formulation of mebendazole resulted in the development of a chewable 500 mg table by Johnson & Johnson (Vermox^{TM}). In the case of young children, the WHO recommends crushing the tablet on a spoon, adding 2-3ml of clean

water and waiting for two minutes until it becomes a soft mass with semi-solid consistency which can more easily be administered. On the other hand, WHO recommends that older children should be encouraged to chew it (but never swallow it whole). Randomized, double-blind, placebo-controlled trials which took place in Ethiopia and Rwanda have established safety and effectiveness against *A. lumbricoides* and *T. trichiura* in children aged 1-16 years [18, 19]. The efficacy of this chewable tablet of mebendazole against hookworm has not yet been studied. This formulation aims at making it easier for pre-school and school-aged children (PSAC and SAC) to swallow the drug but its acceptability has not yet been explored. Thus, in this study we will compare the efficacy, safety, and acceptability and age-appropriateness of the two tablets (swallowable and chewable) of mebendazole and explore caregivers' perceptions about both formulations.

3. Trial objective and purpose

The overall goal of this study is to determine if a chewable formulation of mebendazole is superior to a swallowable formulation tablet of mebendazole (standard of care) against hookworm in children.

We hypothesize that the chewable formulation of mebendazole has a higher efficacy against hookworm infections than the swallowable one. Better absorption and bioavailability as well as better palatability are expected to contribute to superior efficacy.

The **primary objective** of the study is to compare the egg reduction rates (ERRs) of two different mebendazole formulations against hookworm in children (3 - 12 years old): (i) 500 mg of a single chewable mebendazole tablet and (ii) 500 mg of a single solid mebendazole tablet.

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

- To evaluate the safety and tolerability of the two formulations
- To evaluate the CR of the two formulations against hookworm
- To determine the CRs and ERRs against *Ascaris lumbricoides* and *Trichuris trichiura*
- To investigate the acceptability and age-appropriateness of both formulation when administered to children between 3 and 12 years of age

The **exploratory objectives** of this study are:

- To assess how well caregivers understand the clinical trials aim, procedures, their rights, risks and potential benefits

- To compare the effect of different methods of providing information on their understanding of the clinical trial

4. Methodology

4.1. Primary and secondary endpoint

The **primary endpoint** of the study is the ERRs of these two formulations of mebendazole against hookworm assessed before and 14 to 21 days post-treatment using the duplicate Kato-Katz technique. **Secondary endpoints** are the CR against hookworm, CRs and ERRs against *A. lumbricoides* and *T. trichiura* (assessed 14-21 days post-treatment), safety (assessed 3 and 24 hours post-treatment), and acceptability and age-appropriateness of the two formulations of mebendazole (assessed during treatment). **Exploratory endpoints** are how well caregivers understood the clinical trial's informed consent form and its content, and which of the informing methods increase caregivers understanding the most (assessed during the informed consenting process).

4.2. Type of trial

Randomized controlled, open-label, parallel-group, superiority, phase 2 trial.

4.3. Trial design

4.3.1. Baseline survey and screening

This will be a mainly school-based clinical trial that will take place in ***four*** primary schools with kindergarten (Wawi, Mvumoni, Bwagamoyo, Piki ***and Mzambarauni***) on Pemba Island, Tanzania. Children aged 3 to 4 years old may yet be attending school, in which case they will be recruited directly in the communities of the same schools. Children for whom informed consent was obtained will receive an empty container at school, which they should return the following morning with a stool sample. If this first stool sample is positive for hookworm, a second sample will be requested, if possible the next day. Stool samples will be collected and transported by car to the central laboratory in Chake Chake (Public Health Laboratory Ivo de Carneri, PHL-IdC), if possible the next day. The stool sample collection will be done on different days to adequately cover the egg shedding cycle of 24-48 hours. Sampling will continue until a total of 400 hookworm-infected participants have been identified. Participants may be co-infected with *A. lumbricoides* and/or *T. trichiura*. The prevalence for hookworm

infected individuals is expected to be between 30% and 50% [20-23], hence we anticipate screening around 800-1,300 individuals to reach the total number of participants. The number of screened individuals will depend on the prevalence of the parasite.

All stool samples will be prepared and analysed in the PHL-IdC on Pemba, United Republic of Tanzania. The Kato-Katz technique will be used for the quantitative assessment of STH infections. A first stool sample will be collected from each participant and if the participant is found positive for hookworm a second stool sample will be requested, if possible the next day. From each stool sample duplicate Kato-Katz thick smears (41.7 mg each) will be prepared [24]. All Kato-Katz thick smears will be microscopically analysed by experienced technicians within the first 60 minutes and will then be destroyed within a few days (after passing the quality control). A subsequent independent quality control of sample results for hookworm and concomitant STH will be conducted (described in section 4.3.2).

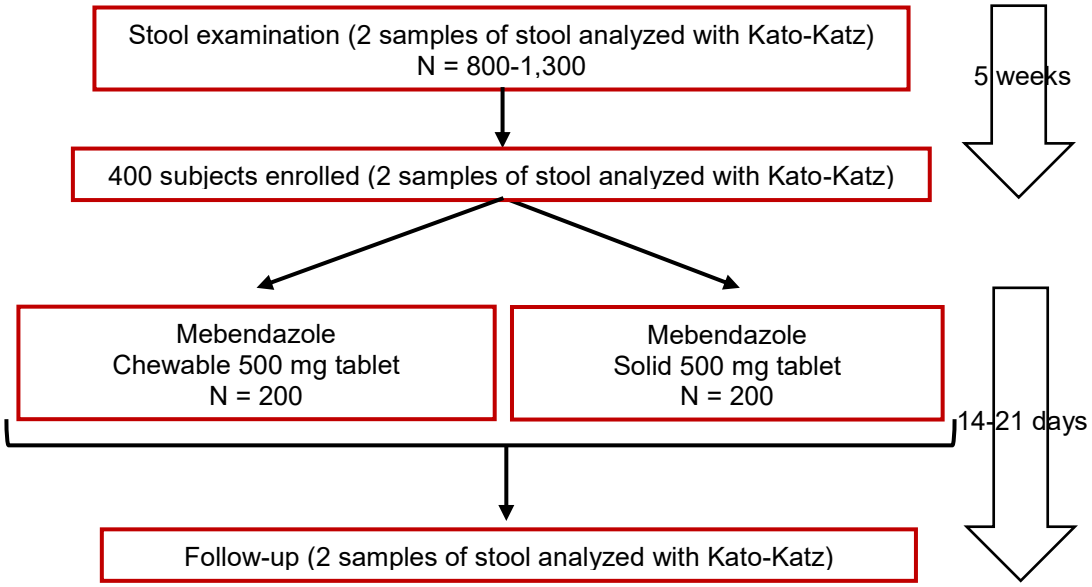

Figure 1: Mebendazole efficacy study-flow.

Participants found to be positive for hookworm and eligible (hookworm eggs per gram of stool (EPG) > 100 and more than one slide with hookworm eggs), will be invited for the physical and clinical examination day which will either take place the day before treatment or on the treatment day itself, but before treatment. All invited subjects will visit one of the study physicians and nurses to undergo a physical examination. Participant's medical history, haemoglobin levels (using HemoCue), and, in the case of female participants, a pregnancy test (girls aged ≥ 10 years will be asked to provide a urine sample) will be recorded. Severely anaemic participants (below 70 g/l Hb in children aged 6-59 months and below 80 g/l Hb in children aged 5-12 years, according to WHO definition) and pregnant girls will be excluded.

Pregnant participants will be given the option of receiving a similar looking tablet which does not contain any drug to avoid any stigmatization and severely anaemic participants will receive the combination of ivermectin and albendazole (according to WHO recommendations).

4.3.2. Kato-Katz slide reading quality control

To ensure quality of hookworm diagnosis, 10% of the samples will be divided into two stool containers; one of the containers will keep its original participant ID, whereas the second container will be labeled with a new ID (assigned by the co-PI). Duplicate Kato-Katz will be prepared from both containers and the findings compared. For hookworm, results are considered correct if no difference in presence/absence if found. In the case of *A. lumbricoides* and *T. trichiura*, 10% of slides will be re-read by another laboratory technician. Results are considered correct if the following tolerance margin is not exceeded: egg counts are +/-10 eggs for counts ≤100 eggs or +/-20% for counts >100 eggs (for each species separately) [25]. In case discrepancies above the tolerance margin are noted in one or more slides, these slides will be re-read by the local technicians. The new results will be 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 within one day after passing the quality control.

4.3.3. Assessment of efficacy after treatment

The efficacy of the treatment in participants will be determined 14-21 days post-treatment by collecting another two stool samples, which will be microscopically examined for STH using duplicate Kato-Katz thick smears, creating a total of four slides for this time point assessment. Participants will be considered hookworm cured if no eggs were found in the follow-up stool samples.

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 two treatment arms before and after treatment to assess the corresponding ERRs. Individuals will not be included in the trial if the hookworm EPG < 100 (total of the four slides) and/or if there is only one Kato-Katz thick smear slide with a hookworm egg.

Once all follow-up samples have been analysed, all participants who were still found STH-positive will receive albendazole (400 mg single dose) and ivermectin (200 µg/kg), which is currently recommended against STH by the WHO's Essential Medicines List.

4.3.4. Treatment acceptability and age-appropriateness assessment

To compare the acceptability and age-appropriateness of each formulation two methods will be used: (1) an observer will fill in an observational sheet to record the participant's reaction to treatment (Appendix 3) (age-appropriateness), and (2) the participant him/herself (if aged 6 years or older) will respond to a brief questionnaire about the tablet he/she received (acceptability) (Appendix 3).

4.3.5. Caregiver knowledge assessment

In this clinical trial we will embed a parallel study focused on (1) assessing whether caregivers understand the content of the study (and its ICF) and (2) exploring different methods of transmitting the information we intend caregivers to understand before deciding whether their child should participate in our clinical trial and comparing their performance. Caregivers who show up will be randomly assigned to one of four groups with different types of information interventions: (i) no information, (ii) oral information session, (iii) information session with slideshow, and (iv) oral information session plus a theatre. The theatre will be performed by members of the local community with guidance of the research staff regarding its content. Caregivers' understanding will be measured using a short questionnaire which will be pre-tested in a local community (Appendix 5). This questionnaire also includes asset socioeconomic questions.

Interviewers will receive specific training. Caregivers assigned to the control group (no information group) will not have attended any of the three types of information sessions by the time they respond to the questionnaire. However, before they are invited to sign the ICF, they will have to attend an information session with slideshow.

4.4. Measure to minimize bias

Study participants eligible for treatment will be randomly assigned to one of the two treatment arms using a computer-generated stratified block randomization code. The random allocation sequence with varying random blocks of four or eight and stratified by 2 levels of baseline infection intensity (light: 1-1999 EPG, and moderate plus heavy: ≥ 2000 EPG hookworm infections) will be provided by a statistician. Both treatment arms will have an equal number of participants with light infection intensity, although the number of light *versus* moderate/heavy infections are not expected to be equal within each arm, depending on the distribution of infection intensity in the recruited cohort.

4.5. Study duration

The trial is estimated to last 12 weeks with each participant's involvement lasting up to 10 weeks. The screening for the baseline will start about five weeks prior to the treatment. Follow-up screening will take place 14-21 days post-treatment. Schedules of visits are summarized below.

4.6. Schedule of visits

Table 1 briefly presents the distribution of tasks along the trial.

Table 1. Schedule of visits during treatment period.

	Baseline	**Examination/Treatment/Safety**			**Follow-up**	
		Hours				
	Days -35 to -1/0	0	3	24	Days 14 to 21	Days 22 to 29
Sample collection and diagnosis	X				X	
Informed consent	X					
Caregiver questionnaires	X					
Demographics	X					
Medical History		X				
Physical and clinical examination		X				
Hb level and pregnancy assessment		X				
Randomization and treatment		X				

Capturing AEs/ SAEs		X	X	X*	
Administration of ALB+IVM (if still infected at follow-up)					X
Observational sheet	X				

* Passive collection of AEs/SAEs (only when a child/caregiver contacts a staff member).

5. Selection of the trial subjects

5.1. Recruitment

The study will be carried out in preschool- and school-aged children (age: 3-12 years) in ***five*** primary schools with kindergarten (Wawi, Mvumoni, Bwagamoyo, Piki ***and Mzambarauni***) on Pemba, Tanzania, a hookworm endemic area [20-22, 26, 27]. The study will be school-based. Caregivers of potential participants will be invited to participate in an information session where the research staff will explain the purpose and procedures of the study, as well as potential benefits and risks of participating. Particular emphasis will be given to the fact that caregivers should oversee the sample collection to avoid sample mix ups. Caregivers will be encouraged to ask questions in an open discussion forum.

Caregivers interested in having their child/children participate in the study will be invited to complete the process of informed consent by signing the informed consent form (ICF) (Appendix 1). See section 10.3 for further details on obtaining informed consent. Only participants who have written informed consent will be assessed for study eligibility criteria during screening procedures.

5.2. Inclusion criteria

- Male of female children aged between 3 and 12 years;
- Written informed consent signed by caregiver;
- Was examined by a study physician before treatment;
- Provided two stool samples at baseline;
- Hookworm EPG **≥** ***50*** and at least two Kato-Katz thick smears slides with more than one hookworm egg;

5.3. Exclusion criteria

- Pregnant;
- Presence or history of major systemic or chronic illnesses, as assessed by a medical doctor, such as can upon initial clinical assessment;
- Suffers from severe anemia (Hb < 80 g/l);
- Received anthelminthic treatment or metronidazole within past four weeks.
- Attending other clinical trials during the study.

Participants who were diagnosed with hookworm, *A. lumbricoides* and/or *T. trichiura* but were excluded from the clinical trial due to one or several of the above-mentioned exclusion criteria, including withdrawals, will be offered standard anthelminthic treatment (combination of albendazole and ivermectin), except for pregnant girls. In the presence of major systemic or chronic illnesses, besides providing the standard anthelminthic treatment, we will facilitate the best locally available care and/or support.

5.4. Criteria for discontinuation of trial

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

- Withdraws from the study (this can happen anytime as participation is voluntary and there are no further obligations once a participant withdraws); data obtained prior to the withdrawal will be included in the analysis to ensure the validity of the trial. Data of withdrawn participants are filly anonymised once analysis is complete.
- At the discretion of the PI or co-PI, if the participant is not compliant to the requirements of the protocol.

Discontinued subjects will not be replaced. If, for any reason, a subject is discontinued from the study before the end of treatment evaluations, the adverse event (AE) assessment will still be conducted.

5.5. Treatment of subjects

Both mebendazole tablet formulations will be donated by the WHO. Tablets will be kept in their original packing until they are administered to participants. However, we will cut the sheet of encapsulated tablets so that we have them individualized but still in the capsule. To ensure the treatment allocation is concealed, prior to the trial initiation, two subjects independent to the study will prepare sealed, opaque and sequentially numbered envelopes containing the correct encapsulated tablet (chewable or swallowable) for each participant.

On treatment day, one 500 mg tablet will be orally administered to each participant. However, the mode of administration will depend on (i) whether the child is 3-5 year old or 6-12 year old and (ii) on the treatment arm he/she has been allocated to:

- **3-5 year olds** allocated to the **swallowable tablet** arm will be given the crushed tablet on a spoon mixed with a small amount of clean water;
- **6-12 year olds** allocated to the **swallowable tablet** arm will be given the whole tablet to swallow with a glass of clean water;
- **3-5 year olds** allocated to the **chewable tablet** arm will be encouraged to chew the tablet and swallow it without water; if they cannot chew it then a small amount of water will be added to the tablet in a spoon;
- **6-12 year olds** allocated to the **chewable tablet** arm will be encouraged to chew the tablet and then swallow it without water.

The staff administering treatment will be trained in case any child chokes. Treatment arm, date and time will be recorded in the case report form (CRF) (Appendix 2). All drugs will be administered in the presence of at least one study investigator, and ingestion confirmed. The individual observational sheet will be filled out by the co-PI administering the drugs during the treatment of each participant, and as soon as the participant is done with treatment one staff member will pose him/her questions concerning the tablet to explore the acceptability (Appendix 3). This questionnaire will only be administered to the participant if he/she is aged between 6-12 years.

Subjects will be asked not to take any drugs other than those prescribed by the study medical team until they have provided the two follow-up stool samples. After ingestion of the medication, which will be done at school, the subjects will be observed for 3 hours to ensure retention of the drug. Vomiting within one hour post-dosing will require re-dosing. The subjects will not be allowed more than one repeated dose. No re-administration will be needed for subjects vomiting after one hour. The site co-PI is responsible for drug accountability at the study site. Maintaining drug accountability includes careful and systematic study drug storage, handling, dispensing and documentation of administration. Any study product that is unused at the conclusion of the study will be destroyed.

5.6. Concomitant therapy

All medications taken one month before and during the study period until the last stool examination between day 14 and 21 (follow-up) 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 the subjects 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.
- Metronidazole.

6. Safety assessments

Few AEs have been reported following mebendazole administration. The most common reported AEs are abdominal cramps, headache, diarrhoea, fever and fatigue [22, 28, 29]. The chewable mebendazole has previously caused convulsions but only in infants below the age of one year which are not included in this study. The concomitant administration of the chewable mebendazole and metronidazole has caused neutropenia and agranulocytosis [30]. The safety profile of mebendazole will be assessed through the recording, reporting and analysis of baseline medical conditions, a physical examination and active questioning at 3 and 24 hours post-treatment (see section 6.2).

6.1. Adverse event definitions

The term “adverse event” could include any of the following events which develop or increase in severity during the course of the study, after administration of the study product:

- 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;
- 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 as be considered baseline medical conditions. For the purpose of this trial, disease progression and relapse will be considered as treatment failure, not as an AE.

6.1.1. Severity grading

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

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

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 adverse even 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 mebendazole reported in the literature or on the drug package leaflet and listed in the consent form. These AEs are detailed in the drug package leaflet (Appendix 4).

Unexpected adverse drug reaction: Any AE possibly related to the study product 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 (SAEs)

According to the ICH "Clinical Safety Data Management: Definitions and standards for expedited Reporting E2A" [31], a serious adverse event (SAE) includes any event (experience) or reaction in any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening, meaning, the subject 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;
- 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;
- Requires in patient hospitalisation or prolongation of existing hospitalisation;
- Creates a congenital anomaly or birth defect (not relevant for this study);
- Is an important medical event, based upon appropriate medical judgment, that may jeopardize the patient or subject or may require medical or surgical intervention to prevent one of the other outcomes defining serious.

A "severe" adverse event does not necessarily meet the criteria for a "serious" adverse event (SAE). SAE are reported from consent to 24 hours post-treatment. SAE 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 events (SUSARs)

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

Patients will be kept for observation for 3 hours following treatment for any acute AEs. 3h post-treatment participants will be actively questioned about any unfavorable changes in

the subject's condition. Any reported changes will be recorded as an AE, whether reported by the subject or observed by the Investigator. In case of 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. In addition, patients will be also interviewed by a nurse and/or a physician about the occurrence of AEs 24 hours. Information on all AEs (onset, duration, intensity and causality) will be immediately entered in the appropriate AE module of the CRF which is considered as a source document, 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). For all AEs, sufficient information will be pursued and/or obtained so as to permit (i) an adequate determination of the seriousness of the event (i.e. whether the event should be classified as a SAE), (ii) an assessment of the casual relationship between the AE and the study treatments (*i.e.* whether the event should be classified as an adverse drug reaction), and (iii) an assessment of intensity of AEs by the study physician. Additionally, participants will be encouraged to notify study staff of any AEs that may occur outside of scheduled safety assessments. 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 subjects 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 PI and co-PI:

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Socinstrasse 57, 4051 Basel, Switzerland
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Tel.: +255 24 245-23

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E-mail: saidmali2003@yahoo.com

Within the following 48 hours, the local co-PI must provide to study PI further information on the SAE or the unanticipated problem in the form of a written narrative. 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 and ethic committees

The PI will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations. Additionally, this information will be provided to the 'Ethik Komission Nordwest- und Zentralschweiz' (EKNZ, Switzerland) and 'Zanzibar Health Research Institute (ZHRI, Tanzania) according to national rules. Fatal or life-threatening SAEs or SUSARs will be reported within 24 hours to ZHRI, 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.

7. Data management and data quality control

7.1. Source data

Source data are the clinical findings and observations, laboratory data maintained at the study site. Source data are contained in source documents. Local authorities are allowed to access the source data. Source data will be entered directly onto different documents:

- **CRF** where all the clinical and physical examination data, together with treatment information, adverse events and follow-up results are recorded. Each subject enrolled into the clinical study will have a CRF. One of the investigators will review, and approve each completed CRF. All data requested on the CRF must be recorded.

- **Laboratory parasitology sheets** where egg counts for each STH species are recorded.
- **Observational sheet** which an observer will record every child's reaction to treatment (age-appropriateness). Every participant who received treatment will have an observational sheet.
- **Acceptability questionnaire and observation** which the participant responds to if aged between 6-12 years and a staff member fills out (the observation section) for all participants.
- **Consent questionnaire** which every caregiver will respond to assess their understanding of the study their child is enrolled in. This also includes socioeconomic data (asset possession).

All source data documents will be kept for at least 15 years. The study site will retain a copy of the documents to ensure that local collaborators can provide access to the source documents to a monitor, auditor, or regulatory agency.

7.2. Data collection and documentation

Collected data will fall into one of the following categories:

a) Anthropometric and clinical characteristics of the trial participants collected using the study's CRF such as weight, height, blood pressure, temperature, pregnancy status (for female subjects ≥ 10 years of age), overall health status and any abnormal medical condition or disease.
b) Egg counts of hookworm (*Necator americanus* and *Ancylostoma duodenale*, the differentiation of the two species will not be made), *T. trichiura* and *A. lumbricoides*.
c) Observational data concerning the child's receptivity to the tablet.
d) Participant answers to the acceptability and adequacy questionnaire.
e) Asset possession and household characteristics of each participant.
f) Caregivers' answers to the knowledge assessment questionnaire.

Data in above categories (a) and (b) will be paper-captured, whereas data in categories (c), (d), (e) and (f) will be collected directly into tablets using Open Data Kit (ODK; free electronic data collection software) and uploaded to a server hosted at Swiss TPH. In paper-based data collection, all missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked "N/D" will be entered. If the item is not applicable to the individual case "N/A" will be written. All entries will be printed in black ink. All corrections must be initialled and dated. Paper-captured data will be subsequently double entered, using the EpiInfo data entry template, into ACCESS data

entry masks by two independent staff members for quality assurance. The EpiInfo mask will be tested before use. Both databases will then be cross-checked using the Data Compare utility of EpiInfo; any discrepancies will be corrected by consulting the hard copy. Data will be entered at the study site. Data entered into ACCESS databases will only be accessible to authorized personnel directly involved with the study by use of a password. All data will be exported and saved in the following formats: .mdb, .xlsx and .csv. Hard copies of the data such as parasitological sheets and CRFs will remain at PHL-IdC. Digital copies along with the databases will be transferred to the Swiss TPH after a Material Transfer Agreement has been signed by both the Swiss TPH and PHL-IdC. Data will then be analyzed as described in section 8.

7.3. Ethical, legal and security issues

Screened participants will be listed in a confidential “subject screening log” and attributed a unique study ID. The codes will be linked with the participant’s identity on a separate file (subject identification list) and filed in a secured place at PHL-IdC 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 subjects. 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

Each stool sample will be destroyed once a duplicate Kato-Katz thick smear has been prepared. Slides will be destroyed up to one day after the examination and quality control are complete. Data and related material will be preserved for a minimum of 15 years to enable understanding of what was done, how and why, which allow the work to be assessed retrospectively and repeated if necessary. The primary data storage and backup will be in the Swiss TPH shared server and secondary data storage will be: personal laptops of Jennifer Keiser and Marta Palmeirim, Swiss TPH shared server, and SWICTHdrive. All files stored in these locations will be password protected. Archiving conditions will be made strictly confidential by password protection.

7.5. Study documents: translations – reference language

- ICF: Master-document English, all language version are translation thereof.

- Caregiver knowledge assessment questionnaire: Master-document English, all language version are translation thereof.

8. Statistical analysis

8.1. Definition of primary endpoint

The primary endpoint of this study is the ERR of mebendazole against hookworm assessed 14 to 21 days post-treatment using the duplicate Kato-Katz thick smear method.

8.2. Justification of number of trial subjects

Because the primary outcome – difference in egg reduction rates (ERR) – does not follow a known distribution we ran a series of conservative simulations using data from Speich *et al*. [22] to determine the required sample size. An initial round of simulations showed that differences in ERRs are associated with substantial higher power compared to CRs. We used Monte Carlo resampling techniques to simulate CR of 10 and 20%, respectively, which translates roughly into ERRs of 38% and 64%. We estimated that 160 patients per arm are required to detect a statistical significant difference with 80% power. To account for potential loss to follow up (which was low in our previous studies in this setting) of 10% and to include a safety margin of 14% we aim to recruit in total 200 participants per trial arm.

8.3. Description of statistical methods

The primary analysis will use the full analysis set (available case population) according to the intention to treat principle defined as all randomized subjects which provide any follow-up data. Only subjects which were negative at baseline and erroneously randomized will be excluded from the analysis. Palatability and ease of swallowing are critical attributes in children; therefore, a per-protocol analysis will be conducted additionally to disentangle drug efficacy from adherence effects.

Geometric mean egg counts will be calculated for the different treatment arms before and after treatment to assess the corresponding ERRs. The ERR will be calculated as:

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

Bootstrap resampling with 5,000 replicates will be used to calculate 95% confidence intervals (CIs) for ERRs and the difference between the two ERRs. Superiority will be claimed if the 95% confidence interval of the difference in ERRs does not include unity (primary hypothesis).

Differences in CRs will be assessed using unadjusted logistic regressions. In a subsequent analysis an adjusted logistic regression (adjustment for age, sex, weight and strata) will be performed.

AEs will be evaluated descriptively as the difference of proportion reporting AEs before and after treatment.

9. Duties of the investigator

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

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.

All protocol modifications must be documented in writing. A protocol amendment can be initiated by either the PI or any Investigator. The Investigator will provide the reasons for the proposed amendment in writing and will discuss with the PI and Co-PIs. Any protocol amendment must be approved and signed by the 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 subjects, 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 Police Nr. 4746321) and a patient liability insurance will be issued by the National Insurance Cooperation of Tanzania LTD, which will cover any eventual study related injuries or deaths.

9.3. Project management

The trial team will include the PI (Prof. Jennifer Keiser), a trial and data manager (Marta Palmeirim), a trial statistician (Dr. Jan Hattendorf), as well as a physician (Dr. Sauda Kassim Omar), nurses and laboratory technicians. Prof. Jennifer Keiser and Marta Palmeirim 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. Marta Palmeirim will monitor all field activities at the study site. Dr. Sauda Kassim will be responsible for clinical examinations and AEs monitoring. Dr. Shaali Ame and Said Ali (Co-PI in Tanzania) are responsible for supervision of the lab and field technicians, staff management, recruitment monitoring, supply of the material, contact to the local authorities and participating schools to obtain necessary permissions before beginning recruitment.

The investigator team is responsible for ensuring that the protocol is strictly followed. The investigator should not make any changes without the agreement of the PI and co-PIs, except when necessary to eliminate an apparent immediate hazard or danger to a study participant. The investigator will work according to the protocol and GCP. The investigator 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 medical doctor. All entries have to be made clearly readable with a pen. The investigator must be thoroughly familiar with the properties, effects and safety of the investigational pharmaceutical product.

10. Ethical considerations

The investigators have all been trained in GCP. None of the investigators declare to have any conflicts of interest.

10.1. Independent Ethics Committees

The study will be submitted for approval by the institutional research commission of the Swiss TPH and the ethics committees of Switzerland (EKNZ) and Zanzibar (ZHRI). The study will be undertaken in accordance with the Declaration of Helsinki and good clinical practice (GCP).

10.2. Evaluation of risk-benefit ratio

Few AEs have been reported for mebendazole (package leaflet Appendix 4). The most common reported AEs are abdominal cramps, headache, diarrhoea, fever and fatigue [22, 28, 29]. All participants will benefit from a clinical examination and a treatment against STHs. All participants in whose stool we still find hookworm eggs will be treated with the combination of albendazole and ivermectin (according to WHO recommendations).

10.3. Subject information and consent

Community meetings will be conducted to explain to caregivers the purpose and procedures of the study. Caregivers attending this meeting will receive a small provision to cover their costs for transportation (3,000 TSh). Their level of comprehension of the trial's purpose, procedures, risks, benefits and content of the ICF will then be assessed using a short multiple-choice questionnaire. Finally, caregivers of an eligible individual will be invited to sign a written ICF (translated into the local language, *i.e*. Kiswahili) after having had sufficient time for reflection of their child's participation. In case the caregiver is illiterate, an impartial witness that can read and write has to sign the consent and the caregiver has to give a thumb print. 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. Only after the ICF is signed will participants undergo any screening procedures.

10.4. Subjects requiring particular protection

This study will include subjects requiring particular protection: children aged 3-1 years. It is important to include this age group because hookworm infections are common in this age group and they are at high risk of infection. Our trial will produce more evidence to support the search of safer and more effective treatment of STH infections in children.

11. Monitoring and auditing

We will work with a locally based monitor. He/she will conduct site visits to the investigational facilities for the purpose of monitoring the study. Details will be described in a separate monitoring plan. The investigator will permit her/him access to study documentation 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 preventative action plan will be requested and documented in response to any audit observations. No sponsor initiated audits are foreseen, but audits and inspections may be conducted by the local regulatory authorities or ethics committees. The Investigator agrees to allow inspectors from regulatory agencies to review records and is encouraged to assist the inspectors in their duties, if requested.

12. Dissemination of results and publication

The final results of this study will be published in a scientific journal and presented at scientific conferences. The European Research Council 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 conclusions will be shared with the local ethics committee, ZHRI.

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14. Appendixes

Appendix 1. Informed consent form (ICF)

Appendix 2. Case report form (CRF)

Appendix 3. Acceptability questionnaire and observation

Appendix 4. Package leaflets (chewable and swallowable)

Appendix 5. Caregiver knowledge assessment questionnaire