





STUDY PROTOCOL

REVISED **Efficacy and safety of moxidectin and albendazole compared to ivermectin and albendazole co-administration in adolescents infected with *Trichuris trichiura*: a randomized controlled trial protocol [version 2; peer review: 2 approved]**

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Abstract







Background: Infections with soil-transmitted helminths (STHs) predominantly affect impoverished populations in tropical environments. The periodic administration of single dose benzimidazoles (i.e., albendazole, mebendazole) to at-risk individuals in endemic regions is at the center of STH control strategies. Given the low efficacy of these drugs against trichuriasis, investigation of drug combinations including moxidectin and ivermectin has recently been initiated, yet the identification of the best treatment option requires more research. We present the protocol for a trial investigating the efficacy and safety of co-administered moxidectin and albendazole compared to co-administered ivermectin and albendazole against *Trichuris trichiura*.

Methods: We will conduct a randomized controlled trial enrolling 540 *T. trichiura*-infected adolescents aged 12-19 years on Pemba Island (Tanzania). The trial will be open-label with blinded outcome assessors. The primary objective is to demonstrate non-inferiority of orally co-administered single-dose moxidectin (8 mg)/albendazole (400 mg) compared to orally co-administered single-dose ivermectin (200 µg/kg)/albendazole (400 mg) in terms of egg reduction rates (ERRs) against *T. trichiura* infections assessed by Kato-Katz at 14-21 days post-treatment. Secondary objectives include the assessment of the drug combinations' superiority compared to their respective monotherapies, of the cure rates (CRs) against *T. trichiura*, and the safety and tolerability of all treatments, as well as CRs and ERRs against concomitant STH infections (*Ascaris lumbricoides* and hookworm). Potential effects of the treatment regimens on follow-up


Open Peer Review

Reviewer Status  

Invited Reviewers

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Any reports and responses or comments on the article can be found at the end of the article.

prevalences of STH at 5-6 weeks and 3 months post-treatment and pharmacokinetic/ pharmacodynamic parameters will also be assessed.

Conclusions: Results from this trial will help to inform decision- and policymakers on which anthelmintic combination therapy might improve existing deworming programs and provide a valuable adjunct tool for interrupting STH transmission.

Clinicaltrials.gov registration: NCT04700423 (07/01/2021)

Keywords

Trichuris trichiura, Drug efficacy, Drug safety, Tanzania, Ivermectin, Moxidectin, Albendazole, Soil-transmitted helminthiasis

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REVISED Amendments from Version 1

In response to the reviewers' suggestions, the first submitted version of the publication has been changed as follows:

- Information on the blinding has been added both to the Abstract as well as to the "Trial design" section for clarification.
- The introduction was shortened to remove non essential information.
- All information on testing alternative diagnostic methods, i.e. FECPAK⁶² and qPCR, has been removed. The reviewer pointed out correctly that these diagnostics are not tied to the primary objectives of the study and that all outcomes rely solely on standard Kato-Katz microscopy. Removing this secondary objective from the publication helps to avoid confusion. Naturally, the original protocol approved by the ethical committees contains all information about the rationale and procedures (see [clinicaltrials.gov registration NCT04700423](https://clinicaltrials.gov/registration/NCT04700423)). Sections changed: Abstract, Introduction, Research objectives, Outcomes, Laboratory procedures, Data management and data quality control, Discussion
- Medication with known interactions as an exclusion criterion has been removed from [Table 2](#). To our knowledge, no drugs with proven interactions have been reported to any of the study drugs.
- Clarification that all participants will receive a local fatty breakfast has been included in the "Pharmacokinetic studies" section.
- Two references for the assumed CR of ivermectin monotherapy have been added to the "Statistics" section under "Sample size calculation".
- A sentence elaborating on the calculation of ERRs and CRs at the different follow-up time points has been added to the "Statistics" section under "Description of statistical methods".

Any further responses from the reviewers can be found at the end of the article

Introduction

Albendazole and mebendazole are comprehensively used in preventive chemotherapy campaigns to mitigate soil-transmitted helminth (STH) infections. The two benzimidazoles show high cure rates (CRs) against infections with *Ascaris lumbricoides* (both Albendazole and Mebendazole CR 96%) and moderate results against hookworm infections (Albendazole CR 80%, Mebendazole CR 33%). Against *Trichuris trichiura* infections however, neither of them are efficacious (Albendazole CR 31%, Mebendazole CR 42%) and thus fall short in achieving the World Health Organization (WHO) goals of morbidity reduction^{1,2}.

Therapies combining two or more drugs are common in several other treatment areas to protect against drug-resistance as well as increasing and broadening the efficacy in comparison to single treatments³. The combination of ivermectin/albendazole was added to the WHO Essential List of Medicines for the treatment of STH infections in 2017⁴. At this stage, the moxidectin/albendazole combination was classified as second tier priority because moxidectin had not yet been approved⁵.

While for ivermectin/albendazole evidence of superiority compared to single standard treatments in different settings and over varying time points is mounting^{6,7}, only few studies have examined the co-administration of moxidectin and albendazole in STH infections⁸ and to date, no head to head comparison between moxidectin/albendazole versus ivermectin/albendazole has been conducted.

Moxidectin recently got approval by the US Food and Drug Administration (FDA) for the treatment of onchocerciasis at an oral single-dose of 8 mg. Clinical trials carried out by our research group have shown that the combination of moxidectin/albendazole might reveal high potential in the treatment of STH infections^{8,9}. Moreover, the FDA-approved 8 mg dose, both in monotherapy and in combination with albendazole, was found to perform equally well as higher doses of moxidectin against STH species, as shown by our recent dose-finding study against *T. trichiura* infections⁹. It remains to be explored whether the longer half-life of moxidectin ($T_{1/2}$: 491-832 hours)^{10,11} compared to ivermectin ($T_{1/2}$: 16-32 hours; increasing with age)¹² might prove beneficial to the treatment of STH infections and long-term outcomes¹³. The pharmacokinetic/-dynamic (PK/PD) characterization of a drug is essential for the understanding of the human body's response to a drug and *vice versa*. Physiological characteristics like mal- or undernutrition or infection with intestinal worms such as *T. trichiura* potentially affect the PK of a drug^{14,15}. For moxidectin, PK properties have been assessed only in a limited number of studies and not yet in *T. trichiura*-infected participants^{16,17}.

In this paper, we present the protocol for a Phase 3 randomized controlled trial on the efficacy and safety of moxidectin/albendazole combination therapy compared to co-administered ivermectin/albendazole against *T. trichiura* and concomitant STH infections in participants aged 12–19 years. Secondary objectives include the assessment of the drug combinations' efficacies against *T. trichiura* infections compared to monotherapies, as well as the investigation of potential extended effects through a prolonged efficacy assessment scheme (i.e., follow-up at 14–21 days, 5–6 weeks and 3 months post-treatment).

Research objectives

We designed a randomized controlled trial to show non-inferiority of co-administered moxidectin/albendazole compared to co-administered ivermectin/albendazole in participants aged 12–19 years on Pemba Island, Tanzania. From evidence of previous studies conducted by our research group, we expect similar efficacies from the moxidectin/albendazole combination compared to ivermectin/albendazole^{8,9}. Nevertheless, moxidectin might be advantageous in terms of the drug's longer half-life and as an alternative in areas with possible emerging ivermectin resistance^{16,18}. As recommended for new combination therapies, we simultaneously assess superiority of the drug combinations compared to monotherapies.

The primary objective is to demonstrate non-inferiority of co-administered moxidectin (8 mg)/albendazole (400 mg) compared to combined ivermectin (200 µg/kg)/albendazole (400 mg) in terms of egg reduction rates (ERRs) against *T. trichiura* infections assessed by Kato-Katz at 14–21 days post-treatment in

adolescents aged 12–19 years with a non-inferiority margin of 2 percentage-points and 90 power at the 95% confidence interval.

The secondary objectives of the trial are:

- a) to demonstrate superiority against the respective monotherapies in terms of CRs against *T. trichiura* infections assessed by Kato-Katz 14–21 days post-treatment, as this is required for efficacy assessments of combination therapies. Therefore, the trial has five different treatment groups: moxidectin (8 mg)/albendazole (400 mg) combination, ivermectin (200 µg/kg)/albendazole (400 mg) combination, albendazole (400 mg) monotherapy, ivermectin (200 µg/kg) monotherapy and moxidectin (8 mg) monotherapy.
- b) to determine the CRs of the drug regimens against *T. trichiura*.
- c) to evaluate the safety and tolerability of the treatments.
- d) to determine the CRs and ERRs of the treatment schemes in study participants infected with hookworm and/or *A. lumbricoides*.
- e) to investigate potential extended effects of the treatment regimens on follow-up helminth prevalence (5–6 weeks and 3 months post-treatment).
- f) to characterize population PK parameters, as well as potential drug-drug interactions of active study treatments following single and co-administration in *T. trichiura* infected adolescents. If an exposure-response is observed, a PK/PD analysis will further be performed.

This article is reported in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines¹⁹.

Protocol

Trial design

A phase 3 randomized controlled open-label non-inferiority trial with blinded outcome assessors will be conducted among adolescents aged 12–19 years with *T. trichiura* infection. The trial includes one baseline and three follow-up assessments at 14–21 days, 5–6 weeks and 3 months post-treatment (Figure 1). The study is designed as a five-arm trial including two arms with combined treatment through co-administration of separate tablets (arm A; moxidectin/albendazole, arm B; ivermectin/albendazole) and three arms with single drug administration (arm C; albendazole, arm D; ivermectin, arm E; moxidectin).

The efficacy of the treatments will be determined by collecting two stool samples before and at every post-treatment time-point. Each sample will be microscopically examined for *T. trichiura* eggs using duplicate Kato-Katz thick smears. Participants will be eligible if they are positive (≥ 48 eggs per gram

of stool (EPG)) for *T. trichiura* eggs at baseline and will be considered cured at the different follow-up assessments if no *T. trichiura* eggs are found in the stool samples.

Outcomes

Primary outcome. The primary outcome is the ERR of *T. trichiura* egg counts assessed by Kato-Katz microscopy pre-treatment and 14–21 days post-treatment.

Secondary outcomes. The secondary outcomes include CR, defined as conversion from being egg positive pre-treatment to egg negative post-treatment, of *T. trichiura* as well as CRs and ERRs for *A. lumbricoides* and hookworm assessed by Kato-Katz at 14–21 days post-treatment. In addition, tolerability of treatment (type, number and severity of adverse events (AEs)), infection status and intensity derived by Kato-Katz at 5–6 weeks and 3 months post-treatment and PK/PD parameters of the study drugs will be assessed.

Study area and participants

This trial will be implemented as a school-based study on Pemba Island (Zanzibar, on Pemba Island, Tanzania). Secondary schools in areas with moderate to high *T. trichiura* prevalence will be selected based on experience from earlier studies and/or knowledge of the local collaborating teams. These will be Kilindi, Kwale and Ndongoni located in Chake Chake district as well as Kiuyu in Wete district. In each selected school, adolescents aged 12–19 years will be invited for study participation. Entering school over-age is a common occurrence in Zanzibar, thus ages of secondary level pupils may well range from 12 to 19 years of age. Adolescents are within the main target group of helminth control programs and are listed among potential receivers of moxidectin that is, so far, only approved from 12 years of age onwards²⁰.

Study duration

Screening for the baseline is scheduled to start 3 months prior to treatment. Follow-up screenings will take place between 14–21 days, 5–6 weeks and 3 months post-treatment and will last approximately two weeks, respectively. Thus, the maximum time for subject participation will be 6 months. The schedule of visits are summarized in Table 1.

Recruitment

School teachers and caregivers of potential participants and adolescents aged ≥ 18 years 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/children of 12–17 years of age participate in the study or adolescents aged 18–19 years willing to participate will be invited to complete the process of informed consent by signing the informed consent form (ICF)¹⁹. In addition, written assent will be obtained from underage participants. Participants having a signed ICF will be assessed for eligibility.

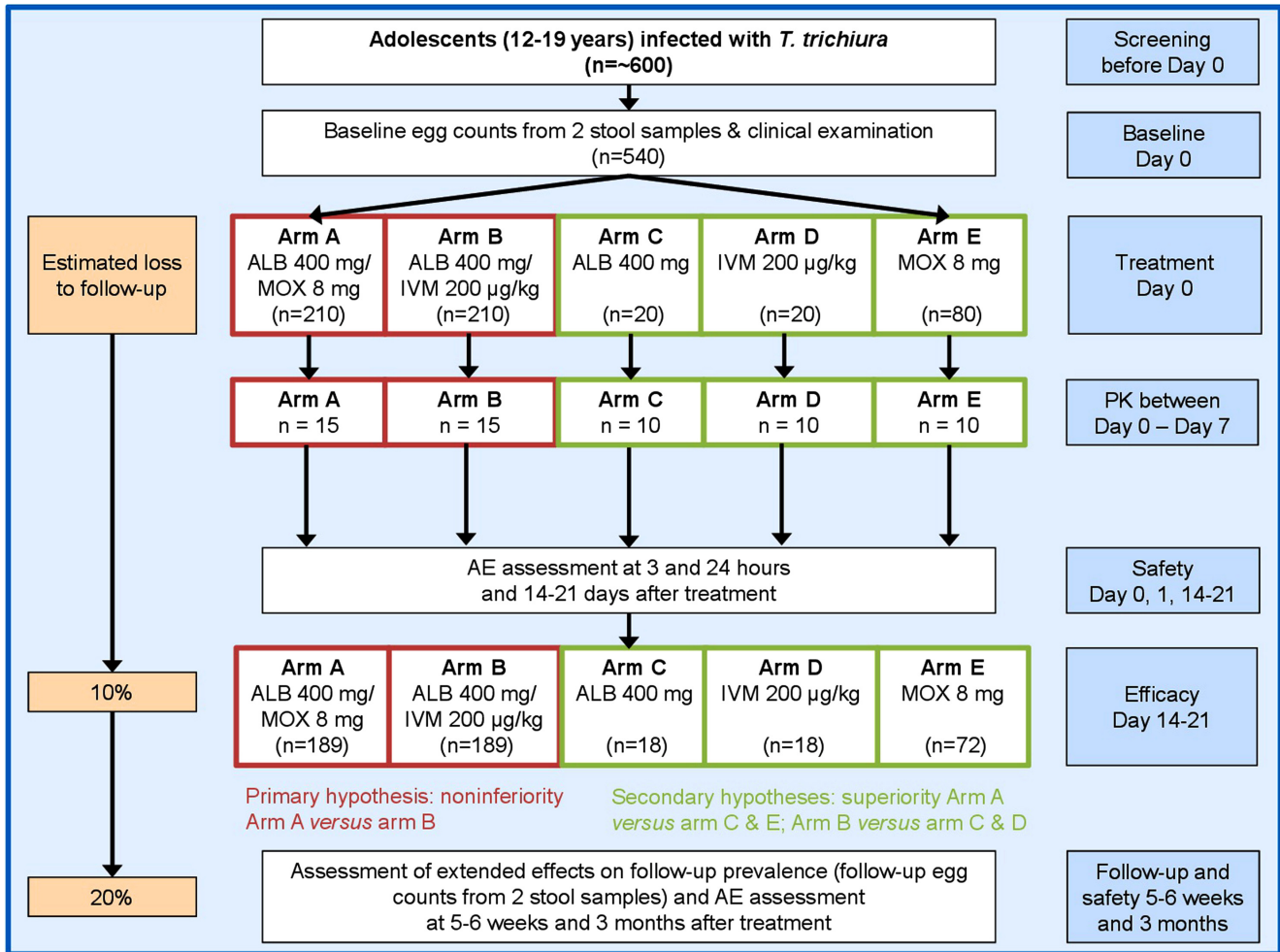


Figure 1. Design and timeline of the randomized controlled trial to be implemented on Pemba Island (Pemba Island, Tanzania). The study is designed as a five-arm trial including two arms with combined treatment through co-administration of separate tablets (arm **A**; moxidectin/albendazole, arm **B**; ivermectin/albendazole) and three arms with single drug administration (arm **C**; albendazole, arm **D**; ivermectin, arm **E**; moxidectin). Abbreviations: ALB, albendazole; MOX, moxidectin; IVM, ivermectin; PK, pharmacokinetics; AE, adverse events.

Laboratory procedures

At baseline, all participants will be asked to provide two stool samples (within a maximum of seven days). From each stool specimen, duplicate Kato-Katz thick smears (41.7 mg each)²¹ will be prepared and examined under a microscope for eggs of *T. trichiura*, *A. lumbricoides* and hookworm by skilled technicians.

For quality control of *T. trichiura* and *A. lumbricoides* egg counts, 10% of slides will be re-read by another laboratory technician. To ensure quality of hookworm diagnosis, 10% of the stool samples will be divided into two sub-samples; 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). An additional Kato-Katz slide will be made

from the second container and the findings compared to the ones from the original sample. For hookworm, results are considered correct if no difference in presence/absence of helminth eggs is found. For *T. trichiura* and *A. lumbricoides* the following tolerance margin should not be 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, the respective slides are examined a third time. The new results are discussed to reach consensus.

The same sampling procedure, diagnostic approach and quality control assessment will be applied at 14–21 days, 5–6 weeks and 3 months post-treatment.

Table 1. Schedule of visits during the study.

	Screening	Baseline/Treatment/Safety				Follow-up		
	Before day 0	0h	3h	24h	6h– 45h	14–21 days	5–6 weeks	3 months
Informed consent	X							
Diagnosis (stool examination)	X					X	X	X
Medical history		X						
Clinical examination		X						
Pregnancy testing		X						X
Hemoglobin measurement		X						
PK (microsampling)		X			X			
Capturing AEs			X	X		X	X	X
Capturing SAE			X	X		X	X	X

Abbreviations: PK, pharmacokinetics; AE, adverse events; SAE, serious adverse events

Eligibility criteria

Participants meeting all inclusion criteria and none of the exclusion criteria (Table 2) will be invited for treatment.

Clinical assessment

A clinical examination of the study participants assessing general health, anthropometric parameters including height and weight as well as forehead temperature using a Braun No touch + forehead NTF3000 (Braun GmbH, Kronberg, Germany) thermometer will precede the treatment. Each participant will be asked to provide a finger-prick blood sample for hemoglobin (Hb) levels, which will be measured using a HemoCue analyzer (Hb 301 system, Angelholm, Sweden). To avoid accidental treatment of pregnant girls/women all female participants will be asked to provide a urine sample for a pregnancy rapid diagnostic test at baseline and at the end of the study (3 months after treatment). Girls/women will be individually counselled that they should not become pregnant during the entire study period. All trial participants will further be asked about chronic diseases and existing clinical symptoms the day of exam, which will be evaluated on relevance with regard to exclusion criteria (Table 2).

Criteria for discontinuation of trial

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

- The subject withdraws from the study: participation is fully voluntary; therefore withdrawal may happen anytime without further obligations.
- At the discretion of the Principal Investigator (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 after treatment but before the end of treatment evaluations, the safety assessment will still be conducted to ensure the discontinued participant's well-being. Data obtained prior to the withdrawal will be included in the analysis to ensure the validity of the trial.

Randomization, concealment and masking

Study participants eligible for treatment will be randomly assigned to one of the five treatment arms using a computer-generated stratified randomization code. The random allocation sequence will be generated by using an algorithm which minimizes deviations from the anticipated arm sizes stratified by 2 levels of baseline infection intensity (light: 1-999 EPG, and moderate/heavy plus heavy: ≥ 1000 EPG *T. trichiura* infections), which will be provided by the trial statistician not involved in enrolment, treatment and data collection. This ensures that all treatment arms will have a similar proportion of participants with light infection intensity. The number of light versus moderate/heavy infections, however, are not expected to be equal in each arm, depending on the distribution of infection intensity in the recruited cohort. Team members conducting the treatment will not know the allocation order. Concealment will be warranted by masking the randomization sequence using envelopes containing the respective treatment arm labels. The study is defined as open-label yet masking is assured since the primary outcome assessors, i.e., the microscopists determining the egg counts for the efficacy assessment, will have no knowledge of the participants' assignment to treatment arms.

Treatment

All eligible *T. trichiura*-infected participants will be treated with the respective single or combination treatment regimen at

Table 2. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
<p>Aged between 12 and 19 years.</p> <p>Written informed consent signed by either parents/caregivers for underage adolescents (aged 12–17 years) or by the participant him/herself (18–19 years of age); and written assent by underage participant.</p> <p>Agree to comply with study procedures, including provision of two stool samples at the beginning (baseline) and on three follow-up assessments (14–21 days, 5–6 weeks and 3 months after treatment).</p> <p>Willing to be examined by a study physician prior to treatment</p> <p>At least two slides of the quadruple Kato-Katz thick smears positive for <i>T. trichiura</i> and infection intensities of at least 48 EPG.</p>	<p>No written informed consent by individual or caregiver and/or no written assent by minors.</p> <p>Presence or signs of major systemic illnesses, e.g. body temperature $\geq 38^{\circ}\text{C}$, severe anemia (below 80g/l Hb according to WHO²²) upon initial clinical assessment.</p> <p>History of acute or severe chronic disease.</p> <p>Recent use of anthelmintic drug (within past 4 weeks).</p> <p>Attending other clinical trials during the study.</p> <p>Pregnancy, lactating and/or planning to become pregnant within the study period.</p> <p>Known allergy to study medications (i.e., albendazole, ivermectin or moxidectin).</p>

Abbreviations: EPG, eggs per gram of stool; Hb, hemoglobin; WHO, World Health Organization

day zero. All regimens are administered orally as a single dose. 400 mg albendazole will be the product of Glaxo Smith Kline (Zentel®) and a single tablet administered. 3 mg tablets of ivermectin will be obtained from Merck (Stromectol®). The weight will be recorded for each participant and the correct dose (i.e., 200 $\mu\text{g}/\text{kg}$) evaluated and administered accordingly. Moxidectin 2 mg tablets will be obtained from Medicines Development for Global Health and 4 tablets administered to each participant. All drugs will be given in the presence of the investigator(s), and ingestion confirmed. This will be recorded with the time and date of administration. Subjects will be asked not to take any drugs other than those prescribed by the study medical team. After ingestion of the medication, the subjects will be observed for 3 hours to ensure retention of the drug. Vomiting and spitting within 1-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 PI and/or 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.

At the end of the study all participants remaining positive for any STH infection will be treated with the currently best recommended treatment (i.e., ivermectin/albendazole against *T. trichiura* and hookworm and albendazole against *A. lumbricoides*).

Pharmacokinetic studies

The PK study will be performed in a maximum of 15 participants in the combination chemotherapy treatment arms (i.e., arms A and B) and 10 participants in the monotherapy treatment arms (i.e., arms C-E), amounting to a subsample of 60 participants overall. All study participants, regardless of participation in PK, will receive a local high-fat breakfast before treatment¹⁷. Since population PK parameters of all three study drugs are available^{23–25}, a sparse sampling approach will be applied to describe the population-based PK profiles of the

individual drugs upon mono- or co-administration. Additionally, potential interference between moxidectin or ivermectin and albendazole will be assessed. For this, capillary blood ($\leq 60 \mu\text{L}$) will be collected by puncture with a finger prick at four time points (approx. 6h, 21h, 27h, 45h post treatment). Two microsamples (duplicates) will be taken at each time point. Each time, the drop of blood will be directly transferred onto Mitra® sticks (Neoteryx, Toronto CA) (10 μL or 30 μL) and/or on Whatman® protein saver cards 903 filter paper (Merck, Darmstadt DE) (30 μL). Mitra® sticks will be utilized for participants having received albendazole and/or moxidectin, whereas filter paper will be used for ivermectin-treated participants. The dried Mitra® sticks and filter paper will be transported to Swiss TPH, Basel, and stored at room temperature until analysis within one month after blood collection. The quantification of the study drugs will be performed using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods as described elsewhere^{23–25}. 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 analyzed for quality control, and the measured concentrations will be used to determine between-run and overall precision and accuracy of the analysis.

Safety assessments

Few adverse events (AEs) have been reported following albendazole, ivermectin or moxidectin single and co-administration in STH-infected individuals. The most common AEs were abdominal cramps, headache, itching, fatigue, nausea, diarrhea, fever and vertigo^{7–9,16,26–28}.

Interviews will be conducted to determine the emergence of clinical symptoms directly before treatment within the scope of baseline assessment. Participants will be kept for 3 hours after treatment administration to observe any possible acute AEs and reassessment will be done at 24 hours post-treatment. The local study physician will perform a full clinical examination if moderate to severe and/or unexpected AEs occur, and

findings will be recorded. An emergency kit will be available on site to treat any medical conditions that warrant urgent medical intervention. At 3 and 24 hours after treatment and retrospectively at days 14–21 as well as 5–6 weeks and 3 months post-treatment, participants will again be interviewed for the assessment of AEs. Information on all AEs (incidence, intensity, seriousness and causality) will be entered immediately in the appropriate AE module of the case report form (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 serious adverse event (SAE)); and; ii) an assessment of the causal relationship between the AE and the study treatments. Intensity of AE will be judged by the study physician (active assessment) or a trained team member (retrospective assessment), following guidelines by the European Medicine Agency (ICH E2A Clinical safety data management: definitions and standards for expedited reporting)²⁹. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. 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 Sponsor-Investigator and co-PIs. Symptoms arising within the time span of 24 hours after treatment and the respective follow-up time points will be monitored passively by teachers or local health workers who will report incidences to the study team. All pregnancies will be reported to the Sponsor-Investigator promptly after becoming aware of the pregnancy. A study physician recruited from a local health facility/hospital will serve as medical contact between the study team and the treating physician or take up the role of treating physician directly. The treating physician will follow-up on the study participant until the end of the pregnancy (either by birth or resolved otherwise). The outcome of the pregnancy will be reported to the Sponsor-Investigator.

Data management and data quality control

Investigators of Swiss TPH and Public Health Laboratory - Ivo de Carneri (PHL-IdC) have agreed on the protocol, performance of study procedures (SOPs from previous studies available on site), CRF completion, specimen collection and diagnostic methods prior to the initiation of the study.

CRF data will be double-entered and compared using [Beyond Compare 4](#) (Scooter Software Inc., Madison, Wisconsin). Any discrepancies will be reviewed against the hard copies of the CRF and corrected accordingly. Electronic data files will be stored on secured network drives with restricted access to study personnel only. Data analysis will be conducted with pseudonymized data and reporting of findings will be fully anonymized.

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 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 subject 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. Laboratory parasitology sheets: Record of the STH egg counts at all sample collection time points
3. PK: Time records of PK samplings for 60 willing participants.

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 (*Necator americanus* and *Ancylostoma duodenale*, no differentiation between the two species will be made) derived from standard Kato-Katz microscopy performed at baseline as well as at 14–21 day, 5–6 weeks and 3 months post-treatment.
- b) 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), overall health status including any abnormal medical condition or chronic disease and AEs.
- c) PK time recording of each sample per person.
- d) Measured concentrations analyzed from micro blood samples and subsequently derived PK/PD parameters.

Data for categories a) to c) will be recorded both paper-based and directly into tablets using [CommCare](#) (Dimagi, Inc., Cambridge, MA) or computers, whereas data in category d) will be captured by software only. Data compiled using the software will be directly saved on the personal, password-protected laptop of one of the Co-PIs and uploaded to a server hosted at Swiss TPH, Basel. In paper-based data collection, all missing data must be explained. If an item 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 noted with the initials of the respective team member and dated. Data in categories a) and b) will be merged into a masterfile and saved in .xlsx, .mdb and/or .csv. Paper-based data will serve as a physical backup and the source data. Data in categories c) and d) will be saved as .mdb, .csv, .xlsx, .txt and/or .pdf files.

Data storage and preservation. All samples will be destroyed after completion of the study. Paper-based and/or 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 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. Electronic source documents will be stored on a flash drive and kept at the study site (IdC PHL, Pemba Island, Tanzania). The primary data storage and backup will be in the Swiss TPH shared server and secondary data storage will be on personal, password-protected laptops. Electronic data files and archiving conditions will be made strictly confidential by password protection.

Ethical, legal and confidentiality issues. Information about study subjects will be kept confidential and managed accordingly. Screened participants will be listed in a confidential “subject screening log” and attributed a unique study ID. In case of enrolment, participants will be listed in a confidential “subject enrolment log”; this document will constitute the only source to decode the pseudonymized data and will only be accessible to the 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.

Statistics

Sample size calculation. For the primary analysis the trial is designed as two arm parallel group randomized controlled trial. We test the primary hypothesis that the treatment combination moxidectin and albendazole is not inferior compared to ivermectin and albendazole. To determine the required sample size, we run a series of simulations using artificial data which behaved roughly in the same way as found by Barda *et al.*⁸. Assuming true ERR of 98% in both arms, we estimate that 160 participants are required in each group to be at least 90% sure that the limits of a two-sided 95% confidence interval (CI) will exclude a difference in favor of the standard group of more than 2 percentage points. To account for a potential loss to follow-up of 10% and including a safety margin of 20% to account for uncertainty in our assumptions underlying the simulations, we anticipate enrolling 210 participants in each combination treatment arm (arm A and B). The secondary hypothesis anticipates superiority of combination therapies against monotherapies. Assuming CRs below 25% for albendazole as well as for ivermectin and 40% for moxidectin monotherapy, we need to enroll 20, 20 and 80 adolescents, respectively, to identify a statistical significant difference with 85% to 90% power (arm C, D, E)^{1,6,9,30-32}. We thus aim to recruit 210 + 210 + 20 + 20 + 80 = 540 participants in total.

The suggested sample size of a maximum of 4 PK time points from 60 willing participants (10–15 per study arm) is sufficiently high to determine the population PK parameters and investigate potential drug-drug interactions with a sparse sampling scheme, considering that PK variability is moderate. A moderate PK variability is a reasonable assumption when dealing with adolescents.

Description of statistical methods. In non-inferiority trials, non-inferiority has to be demonstrated in the intention-to-treat and in the per protocol population. The primary analysis will be performed according to the intention-to-treat principles using the available case population, which includes all participants with any primary end point data. Subsequently, a per-protocol analysis will be performed. Eggs per gram of stool will be assessed by calculating the mean egg count from the quadruplicate Kato-Katz thick smears and multiplying this number by a factor of 24. The geometric mean (GM) ERR will be calculated as:

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

GM egg counts will be calculated for the different treatment arms before and at 14–21 days after treatment to assess the corresponding ERRs. Bootstrap resampling method with 5,000 replicates will be used to calculate 95% CIs for ERRs and the difference between the ERRs.

CRs will be calculated as the percentage of egg-positive adolescents at baseline who become egg-negative after treatment. Differences among CRs will be assessed by using unadjusted logistic regressions. In a subsequent analysis an adjusted logistic regression (adjustment for baseline infection intensity, age, sex, weight) will be performed. ERRs and CRs as well as their respective confidence intervals will be calculated separately for each follow-up. Statistical analysis will be done using R version 4.0.3 (R Foundation, Vienna, Austria).

AEs will be summarized descriptively in tables and figures providing information on clinical relevance, timing, frequency, type, severity and causality by treatment arm.

A nonlinear mixed-effects (NLME) modelling will be used to determine PK parameters including absorption rate (k_a), volume of distribution (V), and clearance (CL). Concentrations are measured with a validated LC-MS/MS method²³⁻²⁵. Using non linear mixed effects, the key population PK parameters will be calculated based on which an effect on the drug-drug interaction might be determined:

- C_{max} maximal plasma concentration
- t_{max} time to reach C_{max}
- AUC area under the curve, from 0 to last time point 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 NLME modeling software Monolix 2018R2 (Lixoft, Antony, France) using compartmental analysis. The elimination half-life will be estimated by the equation: $t_{1/2} = \ln 2 / \lambda$, where λ (the elimination rate constant) will be determined by performing a regression of the natural logarithm of the concentration values during the elimination period.

Ethical considerations

Independent ethics committee. The study has been reviewed and approved by the institutional research commission of the Swiss TPH, the ethics committee in Switzerland: 'Ethikkommission Nordwest- und Zentralschweiz' (AO_2020-00042; date of approval 24 November 2020), and the 'Zanzibar Health Research Ethics Review Committee' (reference no. ZAHREC/03/PR/OCT/2020/23; date of approval 22 October 2020). The study will be undertaken in accordance with the Declaration of Helsinki and good clinical practice. Material transfer agreements between the PHL-IdC and Swiss TPH will regulate the transfer of collected samples.

Evaluation of the risk-benefit ratio. Albendazole, ivermectin and moxidectin are well-known drugs and have little and mainly mild AEs as described to date (e.g., headache, abdominal pain)^{6,9,16,26–28,33}. Albendazole and ivermectin are widely used drugs in mass treatment programs against filariasis while only moxidectin is a relatively new drug, FDA-approved against onchocerciasis³⁴. All community members enrolled in the study will benefit from a clinical examination and a treatment against STHs. All participating subjects remaining positive for *T. trichiura* will be treated with ivermectin (200 µg/kg)/albendazole (400 mg), considering this combination showed higher efficacy compared to the existing standard treatment (albendazole alone) and the recent inclusion of ivermectin-albendazole as recommended treatment scheme against STH on the List of Essential Medicines⁴.

Subject information and consent. Information sessions at the respective schools will be conducted to explain to teachers, caregivers and potential participants the purpose and procedures of the study, as well as potential benefits and risks of participation. All parents or caregivers of eligible adolescents and all participants ≥18 years will be invited to sign a written informed consent sheet. In case the person is illiterate, an impartial witness that can read and write has to sign the consent and the illiterate participant has to give a thumb print. Parents or caregivers and adult participants will have sufficient time for reflection of their child's or their own participation, respectively. Additionally, adolescents (aged 12–17 years) will be briefed verbally, and written assent will be sought in form of their name and signature written down or if illiterate by providing a thumbprint.

Parents or caregivers attending this meeting will receive a small provision to cover their costs for transportation (~US\$ 2). 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.

Quality control and quality assurance

We will work with a locally based external monitor, who 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 them 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 significant deviation. 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.

In our study, no data and safety monitoring board will be established, since we work with well-known drugs in a small sample size and using a single dose treatment. However, advisors will be informed regularly and the findings discussed.

Dissemination of study results and publication

The final results of this study will be published in a scientific journal and presented at scientific conferences. The Bill & Melinda Gates Foundation 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 ZAHREC. After publication, study results will be made available to study communities.

Study status

The screening phase to identify eligible trial participants was initiated in March 2021.

Discussion

Building on our previous work, which identified moxidectin/albendazole as a promising treatment for STH infections and determined the ideal doses^{8,9}, a randomized controlled non-inferiority trial with five treatment arms will be carried out, testing the performance and safety of co-administered moxidectin and albendazole versus combined ivermectin and albendazole treatment. Both combinations will be compared to monotherapy of albendazole, moxidectin and ivermectin. To our knowledge, this trial marks the first randomized controlled trial assessing the safety and efficacy of combined moxidectin/albendazole compared to the recently recommended co-administration of ivermectin/albendazole against STH infections. The evidence from this trial on the efficacy, safety and potentially prolonged infection clearance in adolescents as part of the main target groups may provide further guidance to STH control programs.

Pharmacokinetic evaluations provide critical information about how the individual body responds to the drug, and is most often influenced by dietary habits, gender, age, body mass index, ethnicity, and/or infection type. Our objective is to characterize population PK parameters and drug-drug interactions of the active study treatments after single and co-administration in *T. trichiura*-infected adolescents in on Pemba Island. This study will describe the PK parameters for the first time of any of the study drugs in this population, of ivermectin and moxidectin in this age group and of moxidectin for this infection type overall. The results will inform whether the findings of this study can be directly applied to other treatment cohorts and will

prevent drug failure for predictable reasons in future clinical trials. Drawing from the extensive experience from our research group, the protocol provides the clear outline for a randomized controlled trial that will provide high-quality data on the efficacy and safety of the two drug combinations as well as potential long-term effects. The comparatively long screening time between enrolment of the first participants and treatment may present a limitation, however we anticipate possible fluctuations in egg counts to occur evenly throughout the study group and within the anticipated limits controlled by the inclusion criterion of presenting with at least 48 EPG and positivity on at least two out of four Kato-Katz slides.

Conclusion

This trial aims to inform decision- and policymakers on how and which anthelmintic combination therapy could be introduced into existing large-scale deworming campaigns and thus provide a valuable adjunct tool for interrupting STH transmission and delay potential selection of drug resistance.

Data availability

Underlying data

No data are associated with this article.

Extended data

Open Science Framework: Efficacy and Safety of MOX/ALB vs. IVM/ALB co-administration. <https://doi.org/10.17605/OSF.IO/A3N85>¹⁹.

This project contains the following extended data:

- Additional file 1_WHO-trial-reg-dataset_Moxi-ALB_IVM-ALB_combi_trial_2021-06-11_OSF.pdf (World Health Organization trial registration data set)
- Additional file 2_ICF_Moxi-ALB_IVM-ALB_combi_trial_v1.0_2020-06-15_OSF.pdf (Participant information and consent sheet)

Reporting guidelines

Open Science Framework: SPIRIT checklist for “Efficacy and safety of moxidectin and albendazole compared to ivermectin and albendazole co-administration in adolescents infected with *Trichuris trichiura*: a randomized controlled trial”. <https://doi.org/10.17605/OSF.IO/A3N85>¹⁹.

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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Open Peer Review

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Version 2

Reviewer Report 01 October 2021

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Judd L. Walson 

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The authors have responded to the comments provided by this reviewer. I appreciate the careful attention to the responses and I feel as though the concerns raised have been reasonably addressed and the limitations acknowledged.

Competing Interests: I have received funding from the Bill & Melinda Gates Foundation for trials related to STH elimination.

Reviewer Expertise: Infectious Disease, NTDs, STH, epidemiology, clinical research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 01 October 2021

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All comments and questions have been adequately addressed by the authors. The manuscript is clear and is informative on the justification, aims and methodology.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases, Neglected Tropical Diseases, Clinical Research

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 06 September 2021

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The manuscript by Welsche et al describes the study protocol of a RCT for the treatment of *Trichuris trichiura* infections in adolescents with combination treatment of albendazol with either moxidectin or ivermectin, as well as each of these three drugs as monotherapy. It is a relevant question with implications for the public health control of STH in general and *T. trichiura* in particular. The justification of the trial, study design and selected population are well described and the primary objective with its corresponding outcome measurement are well described.

Comments for the authors:

Suggest including in the abstract and “Trial design” sub sections a mention to the blinded outcome assessor feature of the trial.

The description of the diet to be administered with the treatments should be clarified. It would be useful to include information on the amount of total calories and/or grams of fat content of the “local high fat diet”. It is not clear whether that diet will accompany only the PK participants or the whole study population.

The quality control plan for discordant samples is different for hookworm than for the other

species; could explain the reason for that difference.

Table 2. The exclusion criteria mentioning medication with known interaction with study drugs should include a list of those drugs.

Secondary objectives referring to the comparison between diagnostic methods lacks a description of the methodologic approach to its statistical analysis.

Suggest providing more information on the baseline prevalence reported in the different schools/districts. If there are significant differences between these prevalence, generalized linear mixed models with the school and/or district as random effects should be used, rather than logistic regression, to assess the CRs at the 5-6 weeks and 3 months time points. A description of the analyzes to be carried out at the different time points is also required.

The inclusion of a group receiving ivermectin monotherapy does not appear as justified in order to test any of the relevant questions; but this comment is just a personal view.

Clarify the time interval allowed between both stool samples at screening and at the 3 other time-points (unclear if in the post-treatment visits 1 or 2 samples will be collected).

Suggest including references that endorse the assumed CRs for albendazole and ivermectin monotherapy (Sample size calculation subsection).

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases, Neglected Tropical Diseases, Clinical Research

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 10 Sep 2021

Jennifer Keiser, Swiss Tropical and Public Health Institute, Basel, Switzerland

1. *Abstract and trial design -> mention blinded outcome assessor*

Will be included in version 2

1. *Description of diet*

The information on calories and grams of fat content is unfortunately not available to us as we will get the food fresh from a local cook. We will provide all participants, not just the ones taking part in PK, with two maandazi (comparable to doughnuts) and sugared tea prior to drug administration. This food was chosen after consulting the students on their preferences to make sure participants will really eat what we provided them. A clarification was added in version 2 (please see "Pharmacokinetic studies").

1. *Different quality control plan for discordant results Hookworm vs. T. trichiura / Ascaris*

Hookworm eggs dissolve within a relatively short time after slide preparation, whereas *T. trichiura* and *A. lumbricoides* eggs stay visible. Therefore, hookworm QC has to be done directly after slides are prepared. For logistical and practicality reasons, a separate slide is prepared for hookworm reading instead of disturbing the sample flow by picking out slides. For *T. trichiura* and *A. lumbricoides* however, it is possible to select slides for QC readings after all samples have been processed to have them read the next day. The quality control margins are different for hookworm QC, i.e. only positive or negative, to account for the variance between the original slides and the new slides prepared.

1. *Medication with interactions in exclusion criteria*

This part will be taken out in version 2, it was an artefact from a previous version. Also please see answer to comment 12 of review 1.

1. *Diagnostic methods*

The lack of exact descriptions was due to the experimental nature of the application of FECPAK G2, which was intended to be done as a proof of concept in close collaboration with TECHION, whose technicians are constantly developing the platform. Unfortunately, the Micro-I devices faced technical issues which will make it impossible for us to include the device in the study. See also comment 1 of review 1.

1. *Baseline prevalence between schools and description of analysis as FU timepoints*

We will follow the first suggestion of the reviewer and will provide the main baseline characteristics (age, sex, baseline infection intensity) stratified by school.

With respect to a random effect model the reviewer raised an interesting point. Random effect models are especially recommended in multi-center trials if the number of clusters is high and/or the baseline risk is likely to vary substantially across centers and/or centers are likely to influence patient outcomes. The number of centers in our case is only 4 and neither the baseline risk (geographical proximity) or treatment outcome (same study personnel) is expected to vary noteworthy among centers. However, there is another important point: egg reduction rates cannot be approximated by any theoretical distribution (although zero inflated negative binomial models have been suggested, we do not think that this is appropriate, e.g. because of treatment failures). We construct the confidence intervals using bootstrap re-sampling approach which is difficult to combine with random effects. The reviewer is right that we did not specify which analysis is done at each time point. This is clarified in the revised version.

1. *Ivermectin monotherapy arm*

We had several internal discussions if all trial arms are required but we finally decided to follow the standard guidelines for combination therapies: 'each substance of a fixed combination must have documented contribution within the combination'

1. Time interval allowed between both stool samples

At all time-points, two samples will be collected which should be provided not more than 7 days apart (please see "Laboratory procedures")

1. References endorsing the assumed CRs for ALB and Ivm monotherapy

Will be included in version 2.

Belizario et al., 2003, A comparison of the efficacy of single doses of albendazole, ivermectin and diethylcarbamazine alone or in combinations against *Ascaris* and *Trichuris* spp.

Marti et al., 1996, A comparative trial of single-dose ivermectin versus three days of albendazole for treatment of *Strongyloides stercoralis* and other soil-transmitted helminth infections in children

Competing Interests: We declare that we have no competing interests

Reviewer Report 27 July 2021

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Judd L. Walson

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Updated on 01/10/21 to include a competing interest statement

This paper presents the protocol for a randomized trial of moxidectin/albendazole vs. ivermectin/albendazole for the treatment of adolescents with *Trichuris*. The study is timely and will be an important contribution to the literature. Overall, the study is well designed, although there are some minor issues that should be considered.

One major concern is the attempt to include a nested study of alternative diagnostics in the trial. The primary endpoint of the trial is dependent on KK and the inclusion of qPCR and FECPAK are really separate exploratory studies that should probably be removed from the primary protocol. I think that these only serve to add confusion to the protocol as it is not entirely clear how discrepancies in results using these various methods would be resolved. I would suggest removing mention of these alternative diagnostics and presenting that as a separate sub-study.

More justification regarding why an alternative 2 drug regimen is needed should be provided. Moxi/alb would likely be significantly more expensive, require a new supply chain, not be part of the existing drug donation program, etc. Given these issues, is non-inferiority even relevant? One might argue that you need to demonstrate superiority to overcome these issues. I think having data on an alternative regimen is worthwhile but these limitations should be discussed.

The introduction should remove the paragraph about the BMGF convening and the desires of the

funding sponsored group. This is not really relevant to the research and the authors should explain the rationale from a scientific need – not a funder driven priority standpoint.

The authors suggest that this would be a phase III study. I think this is more a phase IIb study and would not, on its own, change policy. Consider reframing this as a phase IIb.

The authors should be more clear that this is a single blind study (lab staff are blind to treatment allocation). It is not clear why this was not designed as a double-blind study – this would significantly strengthen the design and I see no rationale for not doing that?

The authors state that participants are eligible if they are positive for trichuris – is this in either of the two samples or in both?

More detail as to how AEs are being measured is needed. Is this passive – it seems to be somewhat active through the CRFs but more detail is needed.

Having screening 3 months before baseline is problematic and it is not clear why this would be done this way. In addition, at low counts, one would imagine that a sizable fraction of those who screen positive will subsequently be negative at baseline – is this reflected in planning to enroll the necessary sample size?

It is likely that there will be a larger number of participants at the lower range of the age – how is this accounted for in the analysis?

It appears as though discordant sample results are resolved through consensus – this is not terribly scientific. Would encourage clear SOP based rules for resolving discrepancies.

It appears that all girls/women will undergo a pregnancy test and hemoglobins will also be measured. Please provide information about how the results of these tests will be handled? Will parents be told of pregnancy results? There are serious ethical issues to consider here – please expand.

How will concurrent medication use be assessed and which are exclusion criteria?

Given the impact of diet on PK of these drugs, will dietary history be collected?

Please confirm that a DSMC will be assembled and confirm whether an interim analysis will be conducted and if there are any stopping rules for harm?

The fact that the protocol has not been agreed by all investigators (under data management and quality control) is concerning and suggests that the collaborators have not participated fully in the development of this protocol. Please clarify.

Please provide more detail re QA/QC plans for the lab work and the anthropometry.

Please confirm that the trial has been registered on clinicaltrials.gov or similar.

It appears that only individuals with endpoint data will be included – this is a modified ITT.

Everyone randomized should be included in the analysis.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: I have received funding from the Bill & Melinda Gates Foundation for trials related to STH elimination.

Reviewer Expertise: Infectious Disease, NTDs, STH, epidemiology, clinical research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 10 Sep 2021

Jennifer Keiser, Swiss Tropical and Public Health Institute, Basel, Switzerland

1. nested study of alternative diagnostics

We agree with the reviewer's suggestion to remove mention of the alternative diagnostics from this publication. For reference of the original protocol, which received approval from the ethical committees, please consult the registration at clinicaltrials.gov

1. justification regarding why an alternative 2 drug regimen is needed

Non-inferiority is warranted since the goal of the study is not to show that mox/alb is a superior treatment but rather to demonstrate moxidectin to be a valid alternative to ivermectin to broaden the pool of possible treatment options in light of ivermectin being already broadly administered for other parasitic diseases with potential resistance-development in the near future. Mox/Alb might also be useful treating *T. trichiura* infections not responding to iver/alb. Of note, ivermectin is also not a cheap drug and moxidectin will likely be widely used in the future.

1. remove the paragraph about the BMGF convening and the desires of the funding sponsored group from introduction

We agree with the reviewer and removed these sections from version 2.

1. Phase IIb vs. phase III study

Arguably the clinical trial has elements of both phase IIb (limited number of participants and safety regards) and phase III trials (randomization, comparison to standard drug, drug already approved for onchocerciasis, efficacy). The principal and all co-investigator decided on designating it as phase III study in the protocol, which was approved by the ethical

committees.

1. *Single blind*

The study is open-label because both the study subjects and the administering investigator know which treatment is given, however unbiased results are assured by the laboratory technicians being blinded to the allocation. The participants are not explicitly informed of the treatment and they will not know which of the two combination treatments they receive (arms A and B), but by the number of tablets and their size they may be able to detect if they are in a mono-arm or combination arm. Double-blinding or even full single-blinding would have meant having to administer a large amount of placebo pills: an albendazole-placebo as well as moxidectin/ivermectin placebos. We discussed blinding at length internally and deemed it more ethical and practical to reduce the number of pills administered rather than having full blinding.

1. *Trichuris positive:*

Inclusion criteria: a mean epg of at least 48 over both samples and positive in at least two out of 4 Kato-Katz slides

1. *More detail as to how AEs are being measured*

Actively: at 3h and 24h, performed by the study physicians. Passively/retrospectively: at 14-21 days, 5-6weeks and 3months post-treatment, performed by trained study personnel and in case of occurring AEs the study physicians are consulted.

1. *Screening 3 months before baseline*

The screening period was set as three months in the protocol given that this trial will be performed under difficult conditions during a pandemic. Obviously we will try to conduct the baseline screening as quickly as possible. For practicality reasons, treatment will only be done once screening for all potential participants is concluded. Given the historically consistent high prevalence of *T. trichiura* infection in the study population and the minimum requirement of 48epg over two samples, we do not expect spontaneous clearance of infection by beginning of treatment. A safety margin of 20% was included in the sample size calculations.

1. *Larger number of participants at the lower range of age*

In fact, the largest number of participants are likely to be in the medium age range (14-16 years) due to recruitment in secondary schools and the overall high prevalence of *T. trichiura* infections across all age-groups. The analysis does not account for stratification by age or sex. Clinical trials are geared towards internal validity and do not aim at being representative for the whole population. Internal validity is warranted due to equal distribution of age and sex among treatment arms.

1. *Discordant results resolved through consensus*

Slides not passing QC are re-read and results accepted on the basis of all three readings. If the results are discordant after the third reading, the slide is read by the technician performing the QC reading with the microscope connected to a screen to enable all technicians to witness the reading and the result accepted after the final joint reading.

1. *Handling of pregnancy results*

The local Co-PI was consulted to establish the ethically best approach. Unexpected pregnancies are to be discussed privately among the study physicians and the participant. In case of the participant being minor (below 18 years), the caregiver/parent will be informed by the study physician with the participant's wishes being taken into account as

much as possible. The matter will be handled with utmost discretion and results not communicated to anyone but the participant and if minor the caregiver/parent.

1. *Concurrent medication*

The study physicians will assess concomitant medication of each participant prior to treatment during clinical examination. Participants will be excluded if concomitant medication is taken for a severe acute or chronic disease or if anthelmintics have been taken during the last 4 weeks. There are no clinically relevant drug interactions known with any of the study drugs, rare reports of an increased International Normalized Ratio have been reported if ivermectin is co-administered with warfarin. In version 2, this section has been removed (Please see exclusion criteria).

1. *Dietary history*

Participants will be asked to arrive fasted on treatment day, where everyone will receive the same fatty breakfast. The absorption of the drug is directly related to the youngest dietary history, which is why every subject will be treated alike. Fat has been reported to increase the absorption by a factor of two for certain drugs.

Dietary history of more than 12h does contribute to drug metabolism (e.g. malnutrition), as do generally all genetic and environmental factors. This is why it is important to assess PK in different populations.

1. *DSMC*

STH trials can be completed in a few weeks/months, in particular in a high prevalence site such as Pemba, with a treatment phase of just a few days. Furthermore, the study drugs are well known, a DSMB was therefore not assembled in this study.

1. *Protocol not agreed by all investigators*

We do not understand this comment. All investigators have agreed on the protocol prior to study initiation and all collaborators were fully involved in development.

1. *QA/QC details*

Please see sections 'Laboratory procedures' (p. 4-5) and 'Data management and data quality control' (p. 8-9) for detailed descriptions.

1. *Clinicaltrials.gov*

Please see abstract (NCT04700423)

1. *Modified ITT vs. per-protocol*

The reviewer raises an important point. Missing data might result in biased estimates. Several approaches have been proposed to reduce the potential impact of missing data including Expectation Maximization algorithms, Full Information Maximum Likelihood estimation, Multiple Imputation or the less sophisticated Mixed Models for Repeated Measures. Unfortunately, none of these can be used together with egg reduction rates. In addition, previous trials have shown that all observed covariates except baseline infection intensity showed no noteworthy association with the outcome or the the probability of being missing. Therefore, the usefulness of the aforementioned approaches remains questionable. Consequently, we use the next best option the available case analysis. We do not use the term modified ITT because this term, has been used inconsistently and often refers to a per protocol analysis (Abraha et al. 2010 doi.org/10.1136/bmj.c2697). There are good reasons to believe that the available case analysis provides in our case valid estimates: i) the proportion of participants with missing data is expected to be low (around 5%), ii) given the nature of the disease and the usually mild adverse events associated with the

drugs we can assume that most missing data follow a missing completely at random pattern, and iii) in a non-inferiority trial the ITT analysis is not considered the gold standard as in superiority trials but is one analysis which has to be interpreted together with the estimates from the per protocol population.

Competing Interests: We confirm that we do not have any competing interests
