Efficacy and safety of combination moxidectin and albendazole, ivermectin and albendazole and albendazole alone in adolescents and adults infected with *Trichuris trichiura*: a randomized controlled trial

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Funding Agency	Bill and Melinda Gates Foundation		

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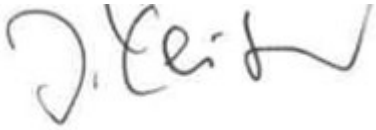
Signature		Date of Signature 06 May 2021
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I have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and will complete the trial within the time designated.

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 fulfill 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.

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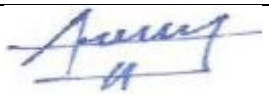
Signature		Date of Signature 06 May 2021
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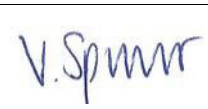
Signature		Date of Signature 06 May 2021
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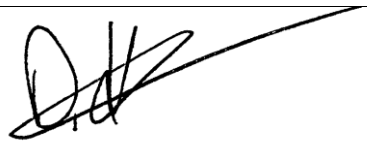
Signature		Date of Signature 06 May 2021
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III. Abbreviations

AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
AIRP	Autorité Ivoirienne de Régulation Pharmaceutique
ALAT	Alanine Amino Transferase
ASAT	Aspartate Amino Transferase
BMGF	Bill & Melinda Gates Foundation
CI	Confidence interval
CNESVS	Comité Nationale d'Éthique des Sciences de la Vie et de la Santé
CR	Cure rate
CRF	Case report form
CSRS	Centre Suisse de Recherches Scientifiques en Côte d'Ivoire
HIV	Human immunodeficiency virus
EKNZ	Ethikkommission Nordwest- und Zentralschweiz
EML	Essential Medicines List
EPG	Eggs per gram
ERR	Egg reduction rate
EU	European Union
FDA	Food and Drug Administration
GCP	Good clinical practice
Hb	Hemoglobin
ICF	Informed consent form
ICH	International council for harmonization of technical requirements for pharmaceuticals for human use
IEC	Independent ethics committee
LC-MS/MS	Liquid chromatography tandem mass spectrometry
MDA	Mass drug administration
MDGH	Medicines Development for Global Health
NLME	Nonlinear mixed-effects
PCR	Polymerase chain reaction
PD	Pharmacodynamics

PI	Principal investigator
PK	Pharmacokinetics
RCT	Randomized controlled trial
RDT	Rapid Diagnostic Test
SAE	Serious adverse event
STH	Soil-transmitted helminth
SUSAR	Suspected unexpected serious adverse reaction
Swiss TPH	Swiss Tropical and Public Health Institute
WHO	World Health Organization

IV. Synopsis

Sponsor/Sponsor-Investigator	Prof. Dr. Jennifer Keiser
Study Title	Efficacy and safety of combination moxidectin and albendazole, ivermectin and albendazole and albendazole alone in adolescents and adults infected with *Trichuris trichiura*: a randomized controlled trial
Short title	Efficacy and safety of MOX/ALB and IVM/ALB vs. ALB alone
Study acronym	MAC CI RCT
Protocol Number, Date and Version	1, 06 May 2021, v2.0
Trial registration	Registered on https://www.clinicaltrials.gov/ (NCT04726969)
Clinical phase	Phase 3 trial
Sample size	282 participants
Indication	*Trichuris trichiura* infection (eggs in stool)
Investigational Product and Reference Treatment	Moxidectin/albendazole and ivermectin/albendazole combination Reference: albendazole
Study Rationale	To provide evidence on the efficacy and safety of co-administered moxidectin and albendazole compared to albendazole monotherapy in adolescents and adults aged 12-60 years against infection with *T. trichiura*. Additionally, to substantiate evidence on the efficacy and safety of co-administered ivermectin and albendazole compared to albendazole monotherapy against *T. trichiura* in the same age group.

Study Objectives	Our **primary objective** is to demonstrate superiority of a) Arm A: moxidectin (8 mg) / albendazole (400 mg) combination, compared to b) Arm B: albendazole (400 mg) in terms of cure rate (CR) against *T. trichiura* infections in adolescents and adults aged 12-60 years assessed at 14-21 days post-treatment by Kato-Katz microscopy. The **secondary objectives** of the trial are: a) to determine the egg reduction rates (ERRs) of moxidectin/albendazole combination therapy compared to albendazole monotherapy against *T. trichiura* b) to determine the CRs and ERRs in *T. trichiura*-infected participants given combined ivermectin (200 µg/kg) and albendazole (400 mg) compared to those given albendazole monotherapy c) to determine the CRs and ERRs of the study drugs against *Ascaris lumbricoides* and hookworm in co-infected participants d) to evaluate the safety and tolerability of the treatment e) to characterize population pharmacokinetics (popPK) and drug-drug interactions of the study drugs albendazole and ivermectin in combination with albendazole in *T. trichiura* infected individuals (aged 12 to 20 years) f) to assess the effect of the gut microbiota on pharmacokinetics parameters and treatment outcome (CRs and ERRs) g) to assess drug-specific off-target effects of anthelmintic treatment on gut microbial communities in post-treatment samples h) to assess the pharmacogenomics of ivermectin and albendazole using whole genome sequencing The **exploratory objective** of this trial is to assess the association between *T. trichiura* infection intensity and blood type.
Study design	Parallel randomized controlled superiority trial
Study product / intervention	Administration of a single oral dose of moxidectin (8 mg) / albendazole (400 mg) or a single dose of ivermectin (200 µg/kg) / albendazole (400 mg)

Comparator(s)	Albendazole (400 mg)
Key inclusion / Exclusion criteria	**Inclusion:** • Individuals aged 12-60 years • having given written informed consent signed by either the participant him/herself (18-60 years) or by caregivers for minors (12-17 years); and written assent by minors • agreeing to comply with study procedures, including provision of two stool samples at screening and at follow-up assessment (14-21 days after treatment) • having at least two out of four Kato-Katz slides positive for *T. trichiura* and a minimum count of 48 eggs per gram (EPG) of stool • able and willing to be examined by a study physician before treatment **Exclusion:** • Presence or signs of major systemic illness • Known or suspected infection with *Loa loa* • History of severe acute disease or unmanaged, severe chronic disease (i.e., condition is not as therapeutically controlled as necessary) • Abnormal liver and kidney function assessed by multiple biochemical blood-based analyses • Recent use of anthelmintic drugs (in the 4 weeks before treatment) • In case of pregnancy, lactation and/or planned pregnancy within the next 3 months • Known allergy to study medication (*i.e.* albendazole, ivermectin or moxidectin) • Prescribed or taking medication with known contraindications and drug interactions with the study medication • Participation in other clinical trials during the study period
Primary Endpoints	• *T. trichiura* infection status of participants given moxidectin/albendazole compared to albendazole alone 14-21 days post-treatment assessed by Kato-Katz

Secondary Endpoints	• *T. trichiura* infection intensity of participants given moxidectin/albendazole compared to albendazole alone 14-21 days post-treatment assessed by Kato-Katz • *T. trichiura* infection status and intensity of participants given ivermectin/albendazole compared to albendazole alone assessed at 14-21 days post-treatment by Kato-Katz • *A. lumbricoides* and hookworm infection status and intensity of co-infected participants given one of the study drugs assessed at 14-21 days post-treatment by Kato-Katz • Adverse events • Characterization of popPK parameters of albendazole and evaluation of possible drug-drug interactions between ivermectin and albendazole and possibly PK/PD parameters of the treatment combinations in *T. trichiura* infected adolescents (aged 12-20 years) • Taxonomic and functional profiling of gut microbial communities using compositional (high throughput sequencing) and quantitative (qPCR) techniques • Characterization of the pharmacogenomics of ivermectin and albendazole in PK participants
Exploratory Endpoints	• Association between *T. trichiura* infection and blood type
Interim Analyses	None
Study Duration	4 months
Schedule	05/2021 of first-participant in (planned) 08/2021 of last-participant out (planned)
Study centres	Dabou and Jacqueville districts, Côte d'Ivoire
Measurements & procedures	Two stool samples will be collected, if possible, on two consecutive days. The medical history of the participants will be assessed with a standardized questionnaire, in addition to a clinical examination carried out by the study physician before treatment. All participants will be interviewed before treatment and after 3 and 24 hours (active surveillance) and retrospectively again at 14-21 days for

	the occurrence of adverse events (AEs). Any potential AEs happening between 24 hours and the respective follow-up time points will be monitored passively and medical intervention provided if necessary. The efficacy of the treatment will be determined at 14-21 days post-treatment by collecting another two stool samples. All stool samples will be examined with duplicate Kato-Katz thick smears for *T. trichiura*, *A. lumbricoides,* and hookworm. For microbiome analyses, *T. trichiura* positive samples as well as 100 STH negative controls (in up to 2 stool samples each at screening and 14-21 days after treatment) will be analyzed. For this purpose, 1-2 g of freshly collected samples will be stored in glycerol and immediately frozen at the field laboratory in Côte d'Ivoire until a frozen shipment to Swiss TPH in Switzerland is arranged for subsequent molecular and microbiological analyses. Each participant will be asked to provide a finger-prick blood sample for blood type determination and hemoglobin measurement at baseline. A venous blood sample (approximately 4 ml) will be taken from each participant at baseline to assess biochemical parameters and blood cell counts. At the same time, anthropometric measurements (i.e. height, and weight) will be taken for all participants. On the day of treatment, participants will be asked to provide a finger-prick blood sample for a malaria test before treatment is administered. In addition, all female participants will be asked to provide a urine sample to determine pregnancy. To determine popPK, possibly PKPD and drug-drug interaction parameters of the study drugs albendazole and ivermectin in combination with albendazole, a subsample of 14 willing study participants (aged 12-20 years) in the two treatment arms (ivermectin/albendazole and albendazole alone) will be asked to provide a maximum of 8 micro blood samples per participant using finger pricks at defined time points between 0 and 24 hours.
Statistical Analyses	An available case analysis according to the intention to treat principles will be performed, including all subjects with primary endpoint data. Additionally, a per-protocol analysis will be conducted. CRs will be calculated as the percentage of egg-positive subjects at screening who become egg-negative after treatment, assessed at 14-21 days with

	quadruple Kato Katz assays. Differences in CRs (between treatment arms) will be analyzed using logistic regression. Geometric and arithmetic mean egg counts will be calculated for the different treatment arms before and after treatment to assess the corresponding ERRs. Bootstrap resampling with 5,000 replicates will be used to estimate 95% confidence intervals (CIs) for ERRs and differences between ERRs. Adverse events will be compiled into frequency tables and compared between treatment groups using descriptive summary statistics. To determine popPK, PK/PD and drug-drug interaction parameters, nonlinear mixed-effects (NLME) modeling will be used. The association between blood type and infection intensity will be analyzed using logistic regression. Microbial communities will be analyzed for within sample (alpha)-diversity (observed taxa, Shannon diversity, phylogenetic diversity, Berger-Parker dominance); between sample (beta)-diversity (Bray-Curtis dissimilarity, weighted and unweighted UniFrac distance), sample community composition (presence/absence and relative abundance of key taxa, most abundant taxon) and aggregate community composition (prevalence and relative abundance of key taxa, core microbiota).
GCP statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ICH-GCP E6 (R2) as well as all national legal and regulatory requirements.
Key explanation for the inclusion of children	This study will involve adolescents of at least 12 years of age, since an infection with *T. trichiura* occurs most often in children who are therefore the main target group of deworming campaigns. Younger children will not be included as moxidectin is registered only for children ≥ 12 years.
Recruitment procedure	The trial will be conducted in Dabou and Jacqueville districts, Côte d'Ivoire. It will take place in areas with moderate to high *T. trichiura* endemicity (communities with a prevalence ≥ 10%) identified from earlier studies and/or based on experience of the local collaborating team.

Coverage of damages	Winterthur, Police Nr. 4746321; L'Africaine des Assurances Côte d'Ivoire, Police Nr. 2020-12-8218320
Storage of data and samples for future research aims	After the study has been completed, all samples will be destroyed. Case report forms and electronic source data will be kept for a minimum of 20 years.
Conflict of interest in relation to the investigated drugs	We declare no conflict of interest in relation to the investigated drugs.

2. Background information

Albendazole and mebendazole are the most widely used drugs for preventive chemotherapy campaigns against soil-transmitted helminth (STH) infections. Albendazole is characterized by high cure rates (CRs) against infections with *Ascaris lumbricoides* (96%) and moderate CRs against hookworm infections (80%). Despite the use of albendazole as part of mass drug administration (MDA) campaigns in endemic settings, lower efficacy of albendazole is observed against *Trichuris trichiura* infections (CR 31%) [1, 2].

Therapies combining two or more drugs are widely advocated in different therapeutic areas such as tuberculosis, malaria, HIV/AIDS or cancer. The underlying rationale for multifactorial pharmacological treatment varies with the disease and includes the protection against the selection of drug-resistance, and hence, a prolongation of the life-span of effective and available drugs, and to increase and broaden the efficacy over drugs being administered in monotherapy [3].

To help prioritize candidate STH combinations, the Bill & Melinda Gates Foundation (BMGF) defined different levels of investment risk. In more detail, the prioritization includes four tiers and takes into account (i) the current efficacy and safety data of existing anthelmintic drugs; (ii) the financial and time investment required to generate the necessary evidence to change WHO treatment guidelines; and (iii) the potential for transformational change. The ivermectin/albendazole combination was identified as a first-tier priority. Moxidectin/albendazole was classified as second tier priority (since at this stage the drug was not yet approved).

In 2017, ivermectin in combination with albendazole for treatment of STH was added on the Essential Medicines List (EML) paving the way to further evaluate efficacy of this combination among school-aged children and communities in a range of epidemiological settings [4]. While evidence of superiority of combination ivermectin/albendazole compared to single standard treatments is growing [5, 6], efficacy of this combination can vary across settings (unpublished data).

Moxidectin, a macrocyclic lactone, has been an FDA-approved treatment for onchocerciasis and has shown promising efficacy when administering 8 mg in combination with albendazole (CR: 62.5%; ERR: 97.4%) against *T. trichiura* infections in adolescents [7]. A review of available data suggests that the high fat solubility, long half-life, intrinsic potency and high safety margin of moxidectin could allow this drug to be used at sufficiently high doses to safely remove ivermectin-resistant parasites. However, there is a need to explore whether moxidectin could reveal a benefit in the treatment of STH infections in settings where efficacy of ivermectin is low [8]. In this trial, we aim to evaluate if moxidectin in combination with albendazole is an efficacious treatment against *T. trichiura* in Côte d'Ivoire. Furthermore, this trial aims to substantiate the evidence of combined ivermectin/albendazole, since recent trial data suggests no major improvement against trichuriasis (observed CR of 13%).

The pharmacokinetic/-dynamic (PK/PD) characterization of a drug is essential to understand the response of the human body to a drug and vice versa, especially in populations that physiologically

differ from healthy adults. Physiological characteristics like mal- or undernutrition due to intestinal worms, such as *T. trichiura*, can potentially affect the PK of a drug [9, 10]. Age, sex, body weight but also the presence of certain enzymes in different populations are important contributors to the pharmacokinetic profile of a drug. Additionally, pharmacokinetic interaction may occur upon co-administration of different drugs.

A trial currently being conducted by our group will characterize popPK and evaluate PK/PD parameters of albendazole in adults, pre- and school-aged children infected with *T. trichiura*. Our study will be the first one to provide PK information on albendazole in adolescents in this indication. Even more our study will provide essential information on the interaction between ivermectin and albendazole and thus guide optimal drug dosing in *T. trichiura*-infected individuals in Côte d'Ivoire. Moreover, ivermectin and albendazole are substrates for P-gp and CYP3A4, and the bioavailability of drugs can likely be influenced by polymorphisms in both P-gp and CYP3A4. However, extremely limited investigation on the pharmacogenomics of ivermectin have been performed, mainly only in Ghanaian volunteers infected with onchocerciasis treated with ivermectin. No pharmacogenomic differences were found to explain differences between treatment responders and non-responders, but a pharmacokinetic evaluation was not performed and the sample size was extremely limited [11].

Gut microbes have been shown to metabolize a wide range of orally given drugs [12]. Drug-microbe interactions are multifaceted resulting in increased or decreased drug potency as well as modified toxicity of the initial compound [13]. However, their metabolic potential and effect on treatment outcome is not systematically studied, especially their role during first-pass metabolism of xenobiotics. We have generated preliminary data showing the role of the microbiome in treatment efficacy of anthelminthic drugs, including praziquantel and ivermectin (unpublished data) [14]. This study will be the first to assess the role of the gut microbiome in moxidectin-based treatment and will enable us to validate our preliminary observations for ivermectin-based treatment. These observations will be used to assess the potential of new therapeutic opportunities based on the modulation of microbial communities in combination with anthelminthic drugs, to ultimately improve the general efficacy of these important drugs.

3. Trial objective and purpose

We designed a superiority trial to show that co-administered moxidectin and albendazole is superior compared to albendazole monotherapy in individuals aged 12-60 years in the Dabou and Jacqueville districts of Côte d'Ivoire. Moxidectin might be advantageous in terms of the drug's longer half-life and in areas with possible emerging ivermectin resistance [15, 16]. This study will provide further insights on the potential value of moxidectin/albendazole. Our data will pave the way for possible large scale, multi country follow-up studies. Additionally, to substantiate evidence on the efficacy and safety of co-administered ivermectin and albendazole against *T. trichiura*, we include this treatment option as a third

arm in our trial. As recommended for new combination therapies, we simultaneously assess superiority of the drug combinations compared to standard-of-care monotherapy.

The **primary objective** is to demonstrate that co-administered moxidectin (8 mg) / albendazole (400 mg) is superior to albendazole (400 mg) in terms of CRs against *T. trichiura* infections assessed by Kato-Katz at 14-21 days post-treatment in individuals aged 12-60 years.

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

a) to determine the egg reduction rates (ERRs) of moxidectin/albendazole combination therapy compared to albendazole monotherapy against *T. trichiura*
b) to determine the CRs and ERRs *T. trichiura*-infected participants given combined ivermectin (200 µg/kg) and albendazole (400 mg) compared to those given albendazole monotherapy
c) to determine the CRs and ERRs of the study drugs (i.e. albendazole alone, albendazole-ivermectin, albendazole-moxidectin) against *Ascaris lumbricoides* and hookworm in co-infected participants
d) to evaluate the safety and tolerability of the treatment
e) to characterize popPK and drug-drug interactions of study drugs albendazole and ivermectin in combination with albendazole in *T. trichiura* infected adolescents (aged 12-20 years)
f) to assess the effect of the gut microbiota on pharmacokinetics parameters and treatment outcome (CRs and ERRs)
g) to assess drug-specific off-target effects of anthelmintic treatment on gut microbial communities in post-treatment samples
h) to assess the pharmacogenomics of ivermectin and albendazole using whole genome sequencing to determine associations between pharmacogenetic variants with pharmacokinetic or pharmacodynamic parameters

The **exploratory objectives** of this trial is to assess the association between *T. trichiura* infection intensity and blood type.

4. Methodology

4.1 Primary and secondary endpoint

Primary endpoint: *T. trichiura* infection status of participants given moxidectin/albendazole compared to albendazole alone 14-21 days post-treatment assessed by Kato-Katz.

Secondary endpoints:

- *T. trichiura* intensity of infection of participants given moxidectin/albendazole compared to albendazole alone 14-21 days post-treatment assessed by Kato-Katz.
- *T. trichiura* infection status and intensity of participants given ivermectin/albendazole compared to albendazole alone assessed at 14-21 days post-treatment by Kato-Katz.

- *A. lumbricoides* and hookworm infection status and intensity of co-infected participants assessed at 14-21 days post-treatment by Kato-Katz.
- Tolerability of treatment (adverse events (AEs)) assessed at 3 and 24 hour post-treatment.
- Population PK parameters and possible drug-drug interactions between ivermectin/albendazole between 0 and 24 hours post-treatment.
- Gut microbial profiles at screening will be correlated with drug pharmacokinetics parameters and treatment outcomes, and off-target effects of treatment will be measured on microbial communities from stool samples collected at 14-21 days post-treatment.
- Taxonomic relative abundances of gut bacterial communities will be analysed with high-throughput sequencing. Absolute abundances of specific taxa will be measured using taxon-specific qPCR. Changes in relative and absolute abundances will be measured before and at 14-21 days after treatment.
- For the description of genetic variation in the metabolism of ivermectin and albendazole whole genome sequencing will be performed on blood samples collected at baseline from PK participants to determine associations between pharmacogenetic variants with pharmacokinetic or pharmacodynamic parameters.

Exploratory endpoints: Association between *T. trichiura* infection intensity and participants' blood type.

4.2 Type of trial

Parallel randomized controlled superiority trial.

4.3 Trial design

A randomized-controlled trial will be conducted with three treatment arms to be followed-up 14-21 days after treatment (**Error! Reference source not found.**). This trial will be conducted in the Dabou and Jacqueville districts of Côte d'Ivoire. This area was selected, because communities with high endemicity were identified as part of a previous trial on *T. trichiura* in 2019 [17].

The study includes one baseline (day -7 to -1) and one follow-up assessment at 14-21 days after treatment. The study is designed as a parallel two-arm trial with 188 participants aged 12-60 years randomized to either moxidectin (8 mg) and albendazole (400 mg) or albendazole (400 mg) alone. Additionally, approximately 94 individuals aged 12-60 years will be given the combination of ivermectin (200 µg/kg) and albendazole (400 mg) at treatment (day 0) and followed-up at 14-21 days after treatment, resulting in an overall allocation ratio of 1:1:1.

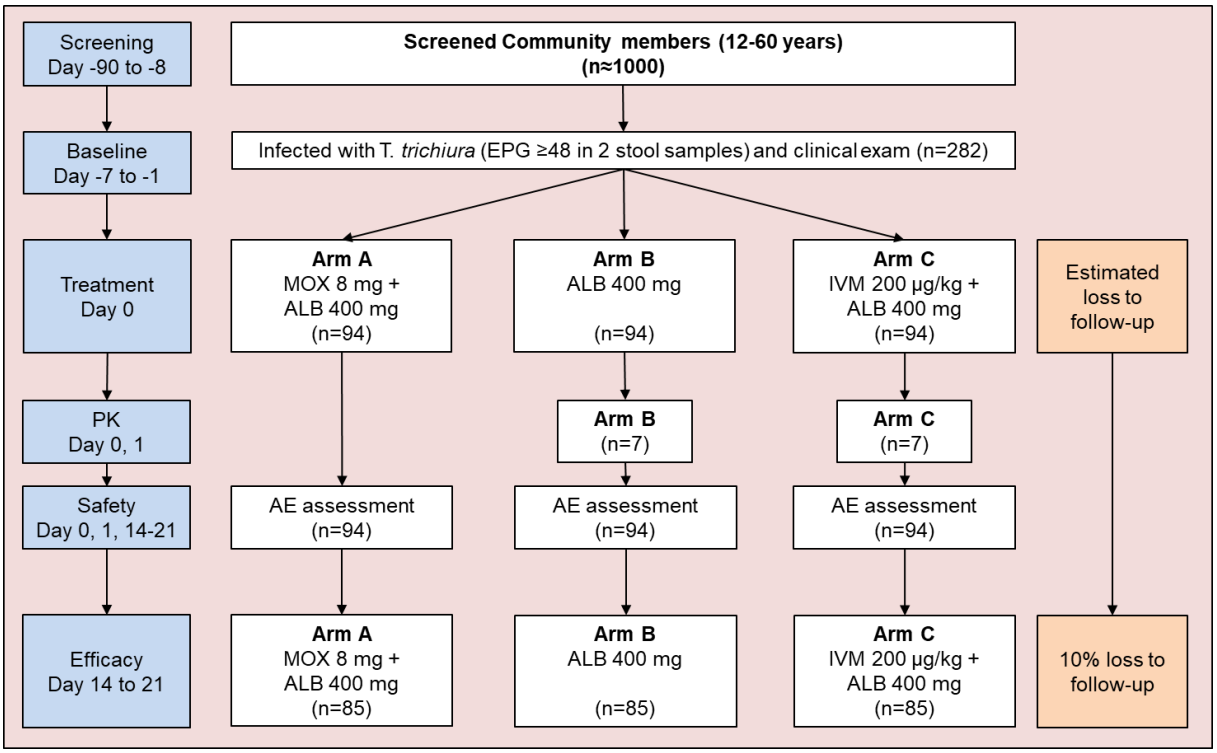

Figure 1. Trial design and timeline.

4.3.1 Diagnosis

At screening, all participants will be asked to provide two stool samples. From each stool specimen, duplicate Kato-Katz thick smears (41.7 mg each) [18] will be prepared and read under a microscope for eggs of *T. trichiura*, *A. lumbricoides* and hookworm by experienced technicians. For quality control of *A. lumbricoides* and *T. trichiura* egg counts, 10% of slides will be re-read by another laboratory technician. Results are considered correct if the following tolerance margin is not exceeded: (i) No difference in presence/absence of *A. lumbricoides* and *T. trichiura* (ii) egg counts are +/-10 eggs for counts ≤100 eggs or +/-20% for counts >100 eggs (for each species separately). In case discrepancies above the tolerance margin are noted in one or more slides, the respective slides are re-read by the local technicians. The new results are discussed, so that in case of discordant results, slides can be re-evaluated to reach consensus. All microscopically analyzed quadruplicate Kato-Katz thick smears will be destroyed after passing the quality control. The same diagnostic approach will be applied at 14-21 days after treatment.

4.3.2 Microbiome stool collection

For microbiome analyses, *T. trichiura* positive samples as well as 100 STH negative controls (in up to 2 stool samples each at baseline and 14-21 days after treatment) will be analyzed. For this purpose, 1-2 g of freshly collected samples will be suspended in 15 mL of sterile phosphate buffer supplemented with 0.1% L-cysteine (PBSc) in a sterile 50 mL falcon tube. The tubes will be left for 5 minutes to let insoluble particles settle. 1 mL aliquots (up to 2 aliquots) of the supernatant will be transferred to sterile cryogenic vials, supplemented with 1 mL of 40% glycerol solution, and subsequently frozen (at -20ºC) until shipment to Swiss TPH in Switzerland is arranged for subsequent molecular and microbiological

analyses. For the microbiome analysis additional data on height and weight of participants will be collected.

4.3.3 Blood type determination

For various infectious diseases the association between blood type and susceptibility to infection as well as infection intensity has been studied [19, 20]. However, there is very limited evidence on this relationship in STH infections, particularly in *T. trichiura* [21]. To investigate the potential association between blood type and *T. trichiura* infection intensity all enrolled participants will be asked to provide a finger-prick blood sample at baseline. Blood type will be determined performing an ABO agglutination test (e.g., using DiaClon/BioRad ID-cards or commercial antisera A, B and D).

4.3.4 Clinical examination

A clinical examination of the study participants assessing general health, anthropometric parameters including height and weight as well as temperature using a non-contact infrared forehead thermometer (Braun No touch – NTF3000; Braun, Kronberg, Germany) will precede the treatment. Each participant will be asked to provide a finger-prick sample to measure hemoglobin (Hb) levels, which will be detected using a HemoCue analyzer (Hb 301 system, Angelholm, Sweden), and to determine blood type (see section 4.3.3). A venous blood sample (approximately 4 ml) will be taken at baseline to assess biochemical parameters, such as urea, creatinine, bilirubin, azotemia, Alanine Amino Transferase (ALAT), Aspartate Amino Transferase (ASAT), as well as blood cell counts (*e.g.* hematocrit, erythrocytes and platelets). Results from baseline biochemical analysis may be reported back to participants during the trial period as seen fit. To avoid accidental treatment of pregnant girls/women all female participants will be asked to provide a urine sample to be subjected to a pregnancy RDT during clinical examination and the day of treatment administration. Before treatment is administered, each participant will be asked to provide a finger-prick blood sample for a rapid diagnostic test (RDT) for *Plasmodium* spp. infection. All trial participants will further be asked about existing clinical symptoms before drug administration using a standardized questionnaire.

4.3.5 Adverse events assessment

Participants will be monitored at the site for 3 hours after treatment administration to observe any possible acute AEs and reassessment will be done at 24h post-treatment. Additionally, interviews will be conducted to determine the emergence of clinical symptoms such as headache, abdominal pain, itching, nausea, vomiting and diarrhea directly before treatment within the scope of baseline assessment. At 3 and 24 hours after treatment and retrospectively at days 14 – 21, participants will again be interviewed for the assessment of AEs. Symptoms arising within the timespan 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. Any symptoms will be recorded in the designated case report form (CRF) and immediate action will be undertaken if indicated.

4.3.6 Assessment of efficacy after treatment

The efficacy of the treatment will be determined 14-21 days post-treatment by collecting another two stool samples, which will be microscopically examined for *T. trichiura* using duplicate Kato-Katz thick smears. Participants will be considered cured if no *T. trichiura* eggs are found in the follow-up stool samples. Eggs per gram will be assessed by adding up the egg counts from the quadruplicate Kato-Katz thick smears and multiplying this number by a factor of six. Geometric and arithmetic mean egg counts will be calculated for the different treatment arms before and after treatment to assess the corresponding ERRs. At the end of the study all participants remaining positive for *T. trichiura* infection will be treated with the currently best recommended treatment of repeated doses of mebendazole (100 mg twice daily over 3 days).

4.3.7 Pharmacokinetic studies

The pharmacokinetic and exposure-response correlation study will be performed in a maximum of 14 adolescents (aged 12-20 years) in the two treatment arms receiving either ivermectin/albendazole or albendazole. The absorption of all study drugs is known to be better after consumption of a high-fat meal, therefore PK participants will receive a local high-fat breakfast before treatment [22]. Since PK population parameters of all study drugs are available [23], a sparse sampling approach can be applied to describe the PK profiles of the individual drugs upon administration as well as a potential interference between ivermectin and albendazole upon co-administration. Within a sparse sampling approach, instead of describing the PK profile for each participant separately, samples are allocated to different time points and/or individuals within the same treatment. Statistical inferences are performed to characterize the population-based PK profile of a specific treatment arm. This approach allows for a reduced number of samplings per treatment arm and renders a PK characterization well tolerable. To this end, a small drop of blood from the fingertip will be taken for a maximum of 8 finger pricks per participant. In total only 14 participants (7 per treatment arm) will undergo PK. The exact time points will cover a timespan of 0 to 24 hours after treatment and will have to be adapted according to a PK model of ivermectin and albendazole currently developed based on data gathered during recent trials involving these study drugs [24, 25]. Capillary blood (≤ 60 µL, i.e. 10 µL for albendazole, and a drop of blood (~ 60 µL) for ivermectin) will be collected by puncture with a finger prick. Two microsamples (duplicates) will be taken with one finger prick. Each time, the drop of blood (10 – 60 µL) will be directly transferred on Mitra® sticks (albendazole) or dried-blood spot cards (ivermectin) [26]. The dried sticks and filter paper will be transported to Swiss TPH, Basel, and stored at room temperature until analysis (< 2 months post-treatment). The quantification of the study drugs will be performed using the validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method as described elsewhere [23, 26]. 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.

From the 14 PK participants whole genome sequencing will be used to determine associations between pharmacogenetic variants with pharmacokinetic or pharmacodynamic parameters. One blood sample (1 ml) for pharmacogenomics will be aliquoted from the venous blood sample collected at enrolment (as described above (4.3.4 clinical examination). Whole blood (1.5 ml) will be dispensed into an EDTA coated tube, inverted six times to mix anticoagulant thoroughly, and transferred by pipette to a cryovial and frozen. Samples will be analyzed at the University of Helsinki in Finland.

4.4 Measure to minimize bias

Study participants eligible for treatment will be randomly assigned to one of the three treatment arms using a computer-generated stratified randomization code. The random allocation sequence with block sizes that will be a multiple of 3 and stratified by 2 levels of infection intensity at screening (light: 1-999 EPG, and moderate plus heavy: ≥ 1000 EPG *T. trichiura* infections) will be provided by a statistician. This way, all treatment arms will have a similar proportion of participants with light infection intensity. Allocation concealment will be warranted using sequential, opaque, sealed envelopes. In the case of accidental unblinding or necessary code breaks, the sponsor will be immediately notified (within 24 hours) and data will be analyzed as set forth in section 8.3. Treatment arm A and B will be double blinded (*i.e.* study participants and the trial team/researchers conducting the treatment and assessing the outcomes will be blinded) using tablets and appearance-matched placebos in bottles relabeled with the respective arm (i.e. A or B) by investigators not involved in efficacy assessment of the trial. Treatment arm C (receiving ivermectin/albendazole) will be an open, unblinded group.

4.5 Study duration and duration of subject participation

The trial will last four months, and screening is scheduled to start three months prior to treatment. The follow-up assessment will take place between 14-21 days after treatment and will last approximately three weeks. Thus, the maximum time for subject participation will be four months. Schedules of visits are summarized below.

4.6 Schedule of visits

Table 1. Schedule of visits of during study.

	Screening	Baseline	Treatment/Safety			Follow up
	Day -90 to -8	Day -7 to -1	Day 0			Day 14 to 21
			0h	Randomization and treatment	3h / 24h	
Informed consent	X					
Diagnosis (stool examination)	XX[1]					XX[1]
Microbiome assessment	X					X
Medical history		X				
Clinical examination		X				
Venous blood assessment		X				
Hemoglobin measurement		X				
Blood typing		X				
Pregnancy testing		X	X			
Malaria RDT			X			
PK (microsampling)			X		X / X	
Capturing AEs					X (active) / X (active)	X
Capturing SAE					X (active) / X (active)	X

[1]: For screening and follow-up assessment two stool samples will be collected and analyzed on two consecutive days.

5. Selection of the trial subjects

5.1 Recruitment

The trial will be carried out in adolescents and adults aged 12-60 years in the Dabou and Jacqueville districts of Côte d'Ivoire. The trial will be implemented as community-based study in communities with endemicity of *T. trichiura* infection above 10% identified during a previous trial. Guardians/caregivers of potential participants aged <18 years and adult participants will be invited to participate in an information session. The research team will explain the purpose and procedures of the study, as well as potential benefits and risks of participation. Attendees will be encouraged to ask questions which will be discussed in an open setting.

Caregivers interested in having their child/children of 12-17 years of age participate in the study or adults aged 18-60 years willing to participate will be invited to complete the process of informed consent by signing the informed consent form (ICF). In addition, written assent will be obtained from underage participants. Participants having a signed ICF will be assessed for eligibility during screening procedures.

5.2 Inclusion criteria

1. Aged between 12 and 60 years.

2. Written informed consent signed by either participant him/herself (18-60 years of age) or by parents/caregivers for underage adolescents (aged 12-17 years); and written assent by underage participant.
3. Agree to comply with study procedures, including provision of two stool samples at the beginning (screening) and at follow-up assessment 14-21 days after treatment.
4. Having at least two slides of the quadruple Kato-Katz thick smears positive for *T. trichiura* and infection intensities of at least 48 EPG.
5. Willing to be examined by a study physician prior to treatment.

5.3 Exclusion criteria

1. Presence or signs of major systemic illnesses, e.g. body temperature ≥ 38°C, severe anemia (below 80g/l Hb according to WHO [27]) upon initial clinical assessment.
2. Known or suspected infection with *Loa loa*.
3. History of severe acute or unmanaged severe chronic disease (*i.e.*, condition is not as therapeutically controlled as necessary).
4. Abnormal liver function assessed by multiple biochemical blood-based analyses
5. Recent use of anthelmintic drugs (in the 4 weeks before treatment).
6. Pregnancy, lactating, and/or planning to become pregnant within the next 3 months.
7. Known allergy to study medications (*i.e.,* albendazole, ivermectin or moxidectin).
8. Prescribed or taking medication with known contraindication to or interaction with study drugs.
9. Participating in other clinical trials during the study period.

5.4 Criteria for discontinuation of trial

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

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

Discontinued participants will not be replaced. If, for any reason, a subject is discontinued from the study before the end of treatment evaluations, the AE assessment will still be conducted. Data obtained prior to the withdrawal will be included in the analysis to ensure the validity of the trial. Data of withdrawn participants are fully anonymized once analysis is complete.

5.5 Treatment of participants

After randomization, all eligible participants will be treated with the respective single or combination treatment regimen according to their assigned treatment arm at day 0. Albendazole will be the product of Glaxo Smith Kline (Zentel®) and a single tablet of 400 mg will be administered. Moxidectin tablets and matching placebo tablets (in terms of appearance) will be obtained from Medicines Development

for Global Health (MDGH), Australia, and four tablets of 2 mg will be administered. Ivermectin tablets (3 mg) will be obtained from Merck (Stromectol®), and administered at a dose of 200 µg/kg based on the recorded body weight of each participant.

The tablets will be handed out from 4 drug containers (moxidectin, ivermectin, placebo and albendazole) according to the randomization list. Each person will receive either:

(i) A single tablet of albendazole plus four tablets of moxidectin

(ii) A single tablet of albendazole plus four tablets of placebo

(iii) A single tablet of albendazole plus 200 µg/kg of ivermectin

All drugs will be administered in the presence of the PI and/or co-PI, and ingestion confirmed. This will be recorded with the time and date of dosing. Participants will be asked to limit the use of any drugs other than those prescribed by the study medical team for the duration of the study as described in section 5.6. After ingestion of the medication, the subjects will be observed for 3 hours to ensure retention of the drug. Vomiting 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 or the co-PIs are responsible for drug accountability at the study site. Maintaining drug accountability includes careful and systematic study drug storage, handling, dispensing, and documentation of administration. Prior to administration, drugs will be stored at room temperature and protected from light and exposure to moisture in a secure area with limited access at the study site.

A study physician will do capillary blood sampling (finger pricking) for the population PK assessment for a maximum of 14 study participants (maximum of 7 adolescents in each of two treatment arms involved in PK) in a quiet location in the community.

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

5.6 Concomitant therapy

All medications taken one month before and during the study period until the last stool examination at the day 14-21 follow-up assessment 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. Participants receiving active anthelminthic concomitant medication during the trial will not be discontinued; however, a case-specific assessment will be done at the point of data-analysis.

6. Safety assessments

6.1 Adverse event definitions

The term "adverse event" is defined as follows:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

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

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

The medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial will not be defined as adverse events but considered as baseline medical conditions. For the purpose of this trial, disease progression and relapse will be considered as failure of prescribed treatment or failure of treatment administration, not as an Adverse Event.

The observation time for adverse events starts when the treatment is initiated until the end of the study. These data will be recorded on the appropriate CRF sections, regardless of whether they are thought to be associated with the study or the drug under investigation. Associated with the use of the drug means that there is a reasonable possibility that the event may have been caused by the drug (see also relatedness definitions below).

6.1.1 Severity grading

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

Grade	Definition
1	Mild: the 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 adverse event and the treatment, known side effects of treatment, medical history, concomitant medication, course of the underlying disease and trial procedures.

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

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

An adverse event 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 adverse event possibly related to the co-administration of ivermectin/albendazole or moxidectin/albendazole reported in the literature or on the drug package leaflets and listed in the consent form.

Unexpected adverse drug reaction: Any adverse event 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

According to the ICH "Clinical Safety Data Management: Definitions and standards for expedited Reporting E2A" [28], a serious adverse event includes any event (experience) or reaction in any untoward medical occurrence that at any dose:

1. results in death;
2. is life-threatening, meaning, the 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;
3. results in persistent or significant disability/incapacity, *i.e.* the event causes a substantial disruption of a person's ability to conduct normal life functions;
4. requires inpatient hospitalization or prolongation of existing hospitalization;

5. creates a congenital anomaly or birth defect (not relevant for this study);
6. is an important medical event, based upon appropriate medical 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. Serious adverse events (SAEs) are reported from treatment until the end of the study.
Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome.
The causality of any SAE that occurs after the study period and its possible relatedness to the study treatment or study participation will also be assessed by investigators as described in section 6.1.2.

6.1.5 Suspected unexpected serious adverse reactions

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

6.2 Methods of recording and assessing adverse events

Few adverse events have been reported following albendazole, ivermectin or moxidectin administration in STH-infected individuals. The most common adverse events were abdominal cramps, headache, fatigue, nausea, diarrhea, fever and vertigo [7, 15, 29-32].
The observation time for AE starts when the treatment is initiated. Subjects will be observed for at least 3 hours following treatment for any acute AE and reassessment will be done at 24h post-treatment. If there is any abnormal finding, the local study physician will perform a full clinical examination and findings will be recorded. An emergency kit will be available on site to treat any medical conditions that warrant urgent medical intervention. Participants will also be interviewed at 3h and 24h actively as well as retrospectively 14 -21 days after treatment about the occurrence of AEs. Any potential AEs happening between 24 hours and the follow-up time point (14-21 days) will be monitored passively and managed with the help of the locally based medical team (including specifically trained community health workers, nurses and medical doctors). Medical intervention will be provided if necessary.
Information on all AEs (incidence, intensity, seriousness and causality) will be entered immediately in the source document, and also in the appropriate AE module of the case report form. For all AEs, sufficient information will be pursued and/or obtained so as to permit i) an adequate determination of the outcome of the event (i.e. whether the event should be classified as a SAE); and; ii) an assessment of the casual relationship between the AE and the study treatments. Intensity of AE will be judged by the study physician, following guidelines by the European Medicine Agency (Note for Guidance on Clinical Safety Data Management).
All SAEs, unexpected adverse drug reactions or SUSARs must be reported as described in Section 6.3.

6.3 Reporting of serious adverse events

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

Prof. Dr. Jennifer Keiser (Sponsor-investigator)
Swiss Tropical and Public Health Institute
Socinstrasse 57, 4051 Basel, Switzerland
Tel.: +41 61 284 82 18
Fax: +41 61 284 81 05
E-mail: jennifer.keiser@swisstph.ch

Dr. Jean T. Coulibaly (Co-PI)
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23 BP 915 Abidjan 23, Côte d'Ivoire
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E-mail: couljeanvae@yahoo.fr

Within the following 48 hours, the local co-investigator must provide to study sponsor-investigator further information on the serious adverse event 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 serious adverse event 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).

All pregnancies in enrolled participants will be reported to the sponsor-investigator within 48 hours of becoming aware of the pregnancy. In the event of pregnancy in a treated participant, she should be monitored until the conclusion of pregnancy. The outcome of the pregnancy and any complications must be reported to the sponsor-investigator within 48 hours.

6.4 Safety reporting to Health Authorities and Ethics Committees

The sponsor-investigator will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations. Additionally, this information will be provided to 'Ethikkommission Nordwest- und Zentralschweiz (EKNZ)' in Switzerland, the 'Comité Nationale d'Éthique des Sciences de la Vie et de la Santé (CNESVS)' and the 'Autorité Ivoirienne de Régulation Pharmaceutique (AIRP)' in Côte d'Ivoire according to national rules. Fatal or life-threatening SAEs or SUSARs will be reported within 24 hours followed by a complete report within 7 additional calendar

days. Other SAEs and SUSARs that are not fatal or life-threatening will be filed as soon as possible but no later than 14 days after first knowledge by the sponsor.

7. Data management and data quality control

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

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 number. Enrolled 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. 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 for study personnel only. Data analysis will be conducted with pseudonymized data and reporting of findings will be fully anonymized.
Essential infrastructure such as a locked room for safe storage of hardcopy data will be made available.

7.1 Source data

Source data are comprised of clinical findings and observations as well as laboratory data maintained and compiled at the study site. Source data are contained in 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. Census: secondary data collected from previously completed census in communities. Holds name, age and sex of each potential participant.
3. Laboratory parasitology sheets: Record of the STH egg counts at all sample collection time points.
4. PK: Time records of PK samplings for 14 willing participants.
5. Laboratory blood and stool analyses: Record of the results of microbiome and/or blood parameters at all sample collection time points.

7.2 Data collection and documentation

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

a) Egg counts of *T. trichiura*, Hookworm (*Necator americanus* and *Ancylostoma duodenale*, no differentiation between the two species will be made) and *A. lumbricoides* derived from standard Kato-Katz microscopy performed at screening as well as at 14-21 days post-treatment.
b) Anthropometric and clinical characteristics of the trial participants collected using the study's CRF such as weight, height, blood pressure, temperature, pregnancy status (for female subjects), overall health status and any abnormal medical condition or chronic disease.
c) Finger prick and venous blood parameters including malaria infection status, hemoglobin, blood type, complete blood count and liver function parameters.
d) Taxonomic and functional profiles will be generated from stool samples using high-throughput sequencing and quantitative polymerase chain reaction. Independently of the employed technique, sample content will be anonymized by removing host related material prior to analysis, e.g. by filtering out host-related sequencing reads.
e) PK time recording of each sample per person.
f) Measured concentrations analyzed from micro blood samples and subsequently derived PK parameters.

All data categories will be recorded paper-based and with the option directly into tablets using CommCare (Dimagi, Inc., Cambridge, MA) or a comparable data-entry software except category e) data that will be captured by software only. For all data except a), the software entries will represent the primary data source. For data category a), data from laboratory parasitology sheets will be entered into CommCare or into a Microsoft Office program (Excel or Access) for data management. 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. 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. Data in all other categories will be saved as .mdb, .csv, .xlsx, .txt and/or .pdf files. Hard copies of the data such as parasitological sheets and CRFs will remain at CSRS. Digital copies along with single databases and compiled masterfiles will be transferred to the Swiss TPH, Basel. 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. In case of enrolment, participants will be listed in a confidential "subject enrolment log" utilizing the same study IDs. The codes will be linked with the participant's identity on a separate file (subject identification list), filed in a secured place at CSRS 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

All samples will be destroyed after completion of the study. Paper-based and electronic source data and related material will be preserved for a minimum of 20 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 (CSRS, Abidjan, Côte d'Ivoire). 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 of Jennifer Keiser, Eveline Hürlimann and Jean T. Coulibaly, and on SWITCHdrive (a cloud storage supported by University of Basel). Electronic data files and archiving conditions will be made strictly confidential by password protection.

7.5 Study documents: translations – reference language

- The protocol master document will be in English and French, all further language versions are translated thereof.
- The ICF master document will be in English and French, all further language versions are translated thereof.

8. Statistics

8.1 Definition of primary endpoint

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

8.2 Justification of number of trial subjects

The primary analysis of this trial aims to assess whether combined moxidectin and albendazole is more efficacious against *T. trichiura* infection compared to standard of care therapy (albendazole monotherapy). We estimate a true CR of 10% for albendazole monotherapy and 30% for combination moxidectin/albendazole against *T. trichiura*. We estimate that enrolling 85 participants per arm will be sufficient to identify a statistically significant difference with 90% power using a two-sided 5% significance level. Additionally, 85 individuals will be included for the ivermectin/albendazole treatment arm to re-evaluate the findings from a previous study with a surprisingly low CR of only 13%. This sample size would allow us to detect the smallest clinically important difference (as defined by our

study panel) of 15%-points with a power of about 75%. To account for a loss to follow-up of 10%, we anticipate to recruit 94 per arm = 282 participants in total.
The suggested sample size of a maximum eight PK samples from 14 willing adolescents (7 per concerned study arm) is sufficiently high to determine the population PK parameters and determine drug-drug interactions with a sparse sampling scheme.

8.3 Description of statistical methods

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. CRs will be calculated as the percentage of egg-positive participants at screening who become egg-negative after treatment. Differences among CRs will be assessed by using unadjusted logistic regressions.
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. The ERR will be calculated as:

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

Geometric mean egg counts will be calculated for the different treatment arms before and after treatment to assess the corresponding ERRs. Bootstrap resampling method with 5,000 replicates will be used to calculate 95% confidence intervals (CIs) for ERRs and the difference between the ERRs.

Previously established nonlinear mixed-effects (NLME) models will be used to compare and determine pharmacokinetic parameters [33]. Concentrations are measured with a validated LC-MS/MS method [23, 26]. Using NLME, the key population PK parameters will be calculated based on which an effect on the drug-drug interaction will be determined:

- C_{max} maximal plasma concentration
- t_{max} time to reach C_{max}
- AUC area under the curve, from 0 to 24h 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. Primary PK parameters including absorption rate (k_a), volume of distribution (V), and clearance (CL) will be estimated utilizing NLME modeling.

The exact design of the sparse sampling scheme will depend on the results of current PK trials of our group.

For the analysis of association between blood type and infection severity, frequency distributions and descriptive summary statistics of the data will be presented by blood type. Crude effect estimates will be presented and adjusted effect estimates will be calculated using uni- and multivariate logistic regression.

9. Duties of the investigator

9.1 Investigator's confirmation

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

9.2 Damage coverage

A general liability insurance of the Swiss TPH is in place (Winterthur, Police Nr. 4746321) and a participant liability insurance has been issued in Côte d'Ivoire (L'Africaine des Assurance, Police Nr. 2020-12-8218320).

9.3 Project management

The trial team will include the PI (Prof. Jennifer Keiser), two Co-PIs (Dr. Eveline Hürlimann and Dr. Jean T. Coulibaly), two Co-investigators (Dr. Pierre H. H. Schneeberger and Dr. Daniela Hofmann), a trial statistician (Dr. Jan Hattendorf) and PhD student, as well as three local physicians whereof one is the local PI (Dr. Yves Koutouan N'Gbesso) and several laboratory technicians. Prof. Jennifer Keiser, Dr. Eveline Hürlimann, Dr. Jean T. Coulibaly, the two Co-investigators and the PhD student 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. Dr. Eveline Hürlimann, Dr. Jean T. Coulibaly and the PhD student 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 communities. Dr. Yves Koutouan N'Gbesso will be responsible for patient recruitment, medical aspects of the trial and enrolment of patients into the trial.
Infrastructure as required for the study needs will be installed as necessary before study launch. The investigator team is responsible for ensuring that the protocol is strictly followed. The investigator should not make any changes without the agreement of the Principal Investigator and the Co-Investigators, 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

10.1 Independent Ethics Committee (IEC)

The study will be submitted for approval by the institutional research commission of the Swiss TPH and the ethical committees of Switzerland and Côte d'Ivoire. The study will be undertaken in accordance with the Declaration of Helsinki and GCP.

10.2 Evaluation of the risk-benefit ratio

Albendazole, ivermectin, and moxidectin are well-known drugs and have little and mainly mild adverse events as described to date (headache, abdominal pain etc.). Albendazole and ivermectin are widely used drugs in mass treatment programs against filariasis and moxidectin is an FDA-approved drug against onchocerciasis. 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 mebendazole 600 mg (to be taken as 6 repeated doses of 100 mg within 3 days), which is considered the most efficacious treatment in settings with potential ivermectin resistance. Participants still showing co-infection with hookworm or *A. lumbricoides* at follow-up assessment will be provided the current standard treatment of albendazole (400 mg).

10.3 Subject information and consent

All parents or caregivers of eligible adolescents and all participants ≥18 years will be asked to sign a written informed consent form. 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, adolescent children (aged 12-17 years) will be briefed verbally, and written assent will be sought in form of their name written down or if illiterate by providing a thumb print.

Information sessions in the respective communities will be conducted to explain to caregivers and potential participants the purpose and procedures of the study. In addition, individual information sessions will take place when visiting potential participants or their parents/caregivers to obtain the written informed consent. Informed consent forms are translated into French and additionally orally explained in local language (*i.e.* Abiji, Adjoukrou and Dida) of the participant if necessary to ensure comprehension. Participation is voluntary and individuals have the right to withdraw from the study at any given point in time with no further obligations. Participation itself will not be awarded with compensation.

10.4 Subjects requiring particular protection

Our study will include adolescents, since *T. trichiura* infection occurs often in children and adolescents; hence this age group is at high risk of infection. Pharmacokinetic/-dynamic analyses in *T. trichiura*-infected adolescents treated with ivermectin/albendazole or albendazole alone have not been conducted to date in this population. The same is true for superiority studies between co-administration of moxidectin/albendazole and albendazole monotherapy. Our trial will produce more evidence to support the search for a safe and effective treatment of STH infections in adolescents and the whole community.

11. Quality control and quality assurance

11.1 Monitoring and auditing

We will work with a locally based external 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 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.

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

In our study, we work with well-known drugs in a small sample size and using a single dose treatment. Nevertheless, the project advisors, Dr André Offiana Touré, parasitologist at the Institut Pasteur de Côte d'Ivoire and Prof Dr Piero Olliaro, infectious disease physician and professor of infectious diseases associated with poverty at Oxford University, United Kingdom, will serve as independent data and safety monitoring board, they will be informed regularly and the findings discussed. This means they have the responsibility to convene, evaluate the study data and give their advice regarding the

continuation or stopping of the study before the treatment, at the end of the study and in case of an important safety event.

12. Funding

Funding for this trial is provided by BMGF (Grant # OPP1153928). This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

13. Dissemination of results and publication

The final results of this study will be published in a scientific journal and presented at scientific conferences. BMGF 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 AIRP. After publication, study results will be made available to study participants.

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