Efficacy and safety of moxidectin in comparison to ivermectin against *Strongyloides stercoralis* infection in adults: a randomized controlled non-inferiority trial

NCT Number: NCT04848688

Document date: 10 February 2022

Study Protocol

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Protocol Number	1		
Version Number	V1.02	**Document Date**	10.02.2022
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Funding Agency	Swiss National Science Foundation (EU-Southeast Asia)		

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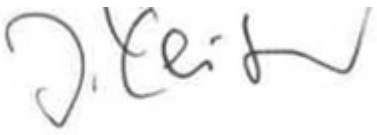
Signature		Date of Signature 10.02.2022
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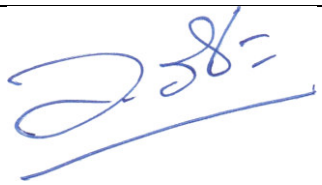
I have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and will complete the trial within the time designated. I will provide copies of the protocol and all pertinent information to all individuals responsible 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.

Co-investigator and Physician

Signature		Date of Signature 10.02.2022
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IV. Synopsis

Study Title	Efficacy and safety of moxidectin in comparison to ivermectin against *Strongyloides stercoralis* infection in adults: a randomized controlled non-inferiority trial
Study Acronym	StrongMoxi
Study Type	Phase 3 trial
Sample size	350
Indication	*Strongyloides stercoralis* infection
Investigational Product and Reference Treatment	Investigational product: moxidectin Reference treatment: ivermectin
Protocol Number, Date and Version	1, 10.02.2022, v1.02
Trial registration	Registered on https://www.clinicaltrials.gov/ (NCT04848688)
Study Rationale	To provide evidence on: Efficacy and safety of an 8 mg dose moxidectin compared to 200 µg/kg dose ivermectin in adults against infection with *S. stercoralis* in Cambodia.
Study Objectives	To determine the efficacy and safety of: 8 mg of moxidectin in comparison to the standard treatment dose of ivermectin (200 µg/kg) in adults infected with *S. stercoralis*. Our **primary objective** is to demonstrate non-inferiority in terms of CR against *S. stercoralis* in adults of an oral 8 mg of moxidectin compared to 200 µg/kg of ivermectin. The **secondary objectives** of the trial are: 1) to evaluate the safety and tolerability of moxidectin 2) to compare the larval reduction rate (LRR) of the two different treatments against *S. stercoralis* 3) to evaluate the CRs of the different treatments against STH co-infections 4) to investigate potential extended effects on follow-up helminth prevalence at 42-49 and 63-70 days post-treatment 5) to relate socioeconomic characteristics (SES), access to sanitation, water facilities, hygiene to baseline infection intensity

	6) to determine the larval excretion pattern until day 28, determined at every second day between day 0 and 28 post-treatment in a subset of 50-100 adults 7) to determine the origin of remaining worm burden after treatment to treatment failure and reinfection based on genetic profiling
Study design	Randomized controlled, double-blinded, 2-arm, parallel group, non-inferiority trial
Study product / intervention	Administration of an oral single-dose of moxidectin (8 mg), or an oral single-dose of ivermectin (200 µg/kg)
Comparator(s)	Ivermectin (200 µg/kg)
Key inclusion / Exclusion criteria	**Inclusion:** Adults (≥ 18-65 years) infected with *S. stercoralis*. **Exclusion:** Any abnormal medical conditions, negative diagnostic result for *S. stercoralis*, no written informed consent by individual. Pregnancy, lactating or planning to become pregnant within the next six months.
Primary Endpoints	CR against *S. stercoralis* at 14-21 days post-treatment derived from larvae per gram (LPG) assessed by quantitative sextuplet Baermann.
Secondary Endpoints	- LRRs against *S. stercoralis* assessed 14-21, 42-49 and 63-70 days post- treatment by quantitative sextuplet Baermann or every second day between day 0 and day 28 by quantitative duplicate Baermann (50-100 adults) - Adverse events - CRs against *T. trichiura, A. lumbricoides*, hookworms or *Taenia ssp.* assessed 14-21 days post-treatment by quadruple Kato-Katz - Genetic profiling of all *S. stercoralis* positive participants (first stool sample at each time point)
Exploratory Endpoints	None
Interim Analyses	None
Study Duration	12 months in total, 16 weeks per participant
Schedule	03/2022 of first-participant in (planned) 02/2023 of last-participant out (planned)
Measurements & procedures	Three stool samples will be collected at baseline analysed in duplicates by a quantitative Baermann method for *S. stercoralis* infection. Co-infection with *T. trichiura*, *A. lumbricoides*, hookworm or *Taenia ssp.* will be identified using duplicate Kato-Katz thick smears on two stool samples. The medical history of

	the participants will be assessed with a standardized questionnaire, in addition to a clinical and physical examination carried out by the study physician shortly before treatment day. Each participant will be asked to provide a finger-prick blood sample for haemoglobin measurements at baseline. Enrolled participants will be treated with either 8 mg of moxidectin or with the standard treatment ivermectin (200 µg/kg). The adults will be interviewed a) before treatment, 3 and 24 hours as well as 14-21, 42-49 and 63-70 days after treatment about the occurrence of adverse events. The efficacy of the treatment will be determined 14-21 days post-treatment. All stool samples will be examined with quantitative sextuplet Baermann assays and quadruplet Kato-Katz thick smears. At 42-49 and 63-70 days post-treatment another three stool samples will be collected and quantified for *S. stercoralis* larvae using Baermann assay to assess potential long-term benefits of the study drugs and treatment regimen. From all positive *S. stercoralis* cases, the larvae will be stored in 70% ethanol and shipped to Australia for sequencing. Of 50-100 adults additional stool samples will be collected every second day between treatment and 28 dayspost-treatment to evaluate larval secretion patterns. To all participating households, a brief questionnaire will be administered assessing information on socioeconomic characteristics (SES) and access to sanitation, water facilities, and hygiene behaviour.
Statistical Analyses	An available case analysis (full analysis set according to the intention to treat principle) will be performed, including all participants with primary endpoint data. Supplementary, a per-protocol analysis will be conducted. CRs will be calculated as the percentage of larvae-positive participants at baseline who become larvae-negative after treatment, assessed 14-21 days post-treatment by sextuplicate Baermann. Uncertainty estimates around the differences among CRs will be assessed using melded confidence intervals with mid-p correction. The non-inferiority margin is set to a 10%-points absolute difference in CR. CRs of coinfections will be calculated as the percentage of egg-positive participant at baseline who become egg-negative after treatment, assessed 14-21 days post-treatment with quadruple Kato Katz assays. LPG will be assessed by calculating the mean of the larvae counts from the Baermann assays and divided by the mean weighted amount of these stool samples. The LRR will be calculated following: (LRR = (1-(LPG at follow-up/LPG at baseline))*100). Geometric and arithmetic mean larvae counts will be calculated for the different treatment arms before and after treatment to

	assess the corresponding LRRs. Bootstrap resampling method with 5,000 replicates will be used to calculate 95% confidence intervals (CIs) for LRRs and differences between LRRs. Adverse events and efficacy outcomes stratified by infection intensities will be compiled into frequency tables and compared between treatment groups using descriptive summaries.
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.
Recruitment procedure	The trial will be conducted in Cambodia in adults aged 18-65. It will take place in areas with moderate to high infection risk in Kampong Chhnang province (prevalence: approx. 41.5%, identified from earlier studies and/or based on experience of the local collaborating teams).
Coverage of damages	Policy No: D/001/CPID/21/000002
Storage of data and samples for future research aims	After the study has been completed, all samples will be destroyed and case report forms, informed consents, source data and trial master file will be kept for a minimum of 15 years (chapter 10).
Conflict of interest in relation to the investigated drugs	We declare no conflict of interest in relation to the investigated drugs.

Abbreviations

AE	Adverse event
CI	Confidence interval
CR	Cure rate
CRF	Case report form
DALYs	Disability-adjusted life years
DF	Dose finding
DSMB	Data and safety monitoring board
EKNZ	Ethikkommission Nordwest- und Zentralschweiz
GCP	Good clinical practice
GLP	Good laboratory practice
Hb	Haemoglobin
ICH	International council for harmonization of technical requirements for pharmaceuticals for human use
IEC	Independent ethics committee
LPG	Larvae per gram
LRR	Larvae reduction rate
NTD	Neglected tropical disease
PI	Principal investigator
RDT	Rapid diagnosis test
SAE	Serious adverse event
STH	Soil-transmitted helminths
WHO	World Health Organization

2. Background information

Over the last decades, increasing evidence has linked major neglected tropical diseases (NTDs) to significant adverse impacts on human and economic development. NTDs affect more than one billion people globally, in particular poor, and marginalized tropical populations, and contribute to an estimated 3.3 million disability-adjusted life years (DALY) lost globally. NTDs also include soil-transmitted helminthiasis such as strongyloidiasis, which is the target of this clinical study [1].

Strongyloides stercoralis is a soil-transmitted nematode belonging to the most neglected infections among the NTDs and found almost worldwide, though with largest prevalence in tropical and subtropical regions, as an example Cambodia [2-4].

Infectious larvae are found in humid soil that is contaminated with faeces. Upon penetration of the intact skin of their host, *S. stercoralis* can reproduce within their human host. This endogenous autoinfection may result in long-lasting infections, which is not seen in other soil-transmitted helminth (STH) infections. Furthermore, *S. stercoralis* is known for its unique and threatening feature to cause systemic infection, which can persist for a lifetime, if appropriate therapy is not administered. *S. stercoralis* infections are typically most intense and debilitating in adults causing significant morbidity [6-8]. However, most infections, particularly chronic low-intensity infections remain non-specific and might be expressed as suffering from malnutrition, physical and cognitive retardation, and reduced work performance [5].

Chemotherapy combined with health education and water, sanitation and hygiene (WASH) programs remain the core to reduce the serious health impacts. The currently advocated treatments by the World Health Organization (WHO) are a single dose of ivermectin or multiple doses of albendazole, while albendazole is less efficacious compared to ivermectin [9, 10]. Since drug pressure is high and resistance is a threat it is of uttermost importance to develop new treatment alternatives. Among new candidates in the human anthelminthic drug development pipeline, moxidectin, a macrocyclic lactone might be a promising alternative. Moxidectin has been recently approved by the Food and Drug Administration (FDA) for use against onchocerciasis (http://www.who.int/tdr/news/2018/moxidectin-approved-as-treatment-for-river-blindness/en/) [11]. Moxidectin offers some advantages over ivermectin. First of all, moxidectin is used weight independent (for onchocerciasis at an 8 mg fixed dose), which renders the administration easier to handle, especially when treating large communities. Second, moxidectin has been shown to have a lower neurotoxic potential than ivermectin [12]. Thirdly, the pharmacokinetic profile of moxidectin in healthy individuals (very long $t_{1/2}$, and a large Vd/F, compared to ivermectin) arises prospects for efficacy also against long-term parasitic activity – as is particularly important when treatment of *S. stercoralis* is desired [13].

Finally, most importantly moxidectin has been successfully used in veterinary medicine against certain ivermectin-resistant strains [14].

Moxidectin was evaluated as an extremely safe drug. A single-dose of 36 mg moxidectin in healthy adults was the highest dose tested to date that still represented a well-tolerated dose [13]. The 1 x 8 mg, therefore, selected, as the highest dose in our study will not pose any health risk. Most common side effects include hypotension, itching, headache, abdominal pain, fever, dizziness or diarrhea. Serious or even fatal encephalopathy may occur in patients co-infected with *Loa Loa*. Furthermore, moxidectin is known to worsen onchodermatitis in patients with hyperactive onchodermatitits. Cambodia is not endemic neither for *Loa Loa* nor onchodermatitits and thus these symptomatic advents shall not constitute a risk in our study. Nevertheless, patients with symptoms for onchodermatitits will be excluded from the study. Additionally, although conclusive teratogenic data on moxidectin are missing, decreased fetal survival and increased fetal born with malfunctions is observed in some animals studies. Thus, pregnant patients as well as females planning to become pregnant within the next six months will strictly be excluded. Last, owing to the lipophilic nature of moxidectin, extraction of moxidectin to the breast milk of nursing mothers is very likely and could be demonstrated in lactating cows [15]. The risk of moxidectin in nursing infants is though unknown, thus breastfeeding females will also be excluded in this study.

In a small exploratory study using the veterinary formulation, a single-dose of 8 mg of moxidectin, and a small sample size (127 participants) moxidectin has been found to be efficacious against *S. stercoralis* (cure rates of 93.7%) and well tolerated in participants [16]. The follow-up phase 2a, randomized, placebo-controlled, dose-escalation trial conducted this year in northern Lao PDR evaluated the efficacy and safety of 2 mg to 12 mg of the human formulation of moxidectin in 209 participants. All tested moxidectin doses showed a promising tolerability with no safety concerns. 4-12 mg of moxidectin displayed a good efficacy profile in the treatment against *S. stercoralis* infections in adults (CR of 83.1%-88.3%). Since the 8 mg dose (CR of 87.0%; 95% CI: 79.8-91.9) is used for onchocerciasis and currently evaluated for other helminth infections this dose was recommended to take forward in phase 2b and phase 3 trials.

In this trial, we will test for non-inferiority of the recommended 8 mg of moxidectin against the standard dose of 200 µg/kg ivermectin.

Moreover, there is a need to explore whether the longer half-life of moxidectin ($T_{1/2}$: 491-832 h) compared to ivermectin ($T_{1/2}$: 16-32 h) could reveal a benefit in the treatment of *S. stercoralis* infections [13, 22]. Potential extended effects will be examined through a prolonged efficacy, safety and tolerability assessment scheme. Thus, additional follow-ups (besides the standard 14-21 days) will be conducted, namely 42-49 days post-treatment in correlation to the duration

of an autoinfection cycle and 63-70 days post-treatment analogous to a second auto-infection cycle as well as the elimination time of moxidectin from blood [13, 23].

Besides the study will be complemented by displaying larval excretion pattern over the whole time course after treatment until 28 days post-treatment and guide more appropriate follow-up periods. The appropriate follow-up time points are today not evaluated for infections with *S. stercoralis*.

Last, strongyloidiasis cannot solely be fought with chemotherapy, yet there is a need for multifaceted approaches including environmental and behavioral adaptation to attain disease control and elimination [30]. This study will be complemented by assessing socioeconomic characteristics, access to sanitation and water facilities as well as hygiene to identify influencing factors with regard to infection intensity and reinfection [30, 31].

Ultimately, results from this trial will inform decision on how moxidectin could be used to treat strongyloidiasis on a patient level and evidence will be strengthened to include moxidectin in the drug armamentarium for future community-wide chemotherapy.

3. Trial objective and purpose

The primary study objectives are

To determine if the efficacy in terms of cure rate of an oral 8 mg of moxidectin is non-inferior to the standard dose of a single oral ivermectin application (200 µg/kg), in 350 *S. stercoralis*-infected adults in Cambodia.

The secondary study objectives are

1.) to determine safety and tolerability of an oral moxidectin dose in 175 adults infected with *S. stercoralis*.
2.) to compare the efficacy based on larvae reduction rates of the different treatments drugs and regimens in 350 adults infected with *S. stercoralis*.
3.) to evaluate the CRs of the different treatments against STH co-infections.
4.) to investigate potential extended effects on follow-up helminths prevalence of the different treatment drugs and regimens around 42-49 and 63-70 days post-treatment.
5.) to relate socioeconomic status (possession of indicator assets), access to sanitation, water facilities and hygiene to baseline infection intensity.
6.) to assess the larval excretion pattern of *S. stercoralis* after treatment with moxidectin up to 28 days post-treatment.
7.) to assess the origin of the larvae positive stool samples by genetic profiling.

4. Methodology

4.1. Primary and secondary endpoint

CR is the primary endpoint. In addition, LRR will be determined and safety and tolerability of treatment evaluated (secondary endpoints). CRs against co-infections are considered as exploratory endpoints.

4.2. Type of trial

Double-blinded, randomized controlled parallel group trial (non-inferiority between 8 mg of moxidectin versus ivermectin, 200 µg/kg) with masked primary outcome assessors.

4.3. Trial design

A randomized trial will be conducted with two treatment arms to be followed-up over a 14-21 follow-up period with additional assessments at 42-49 and 63-70 days after treatment. The trial

will test for non-inferiority of a 8 mg dose of moxidectin versus ivermectin 200 µg/kg with a margin of 10%-points.

The study cohorts are presented in the figure below:

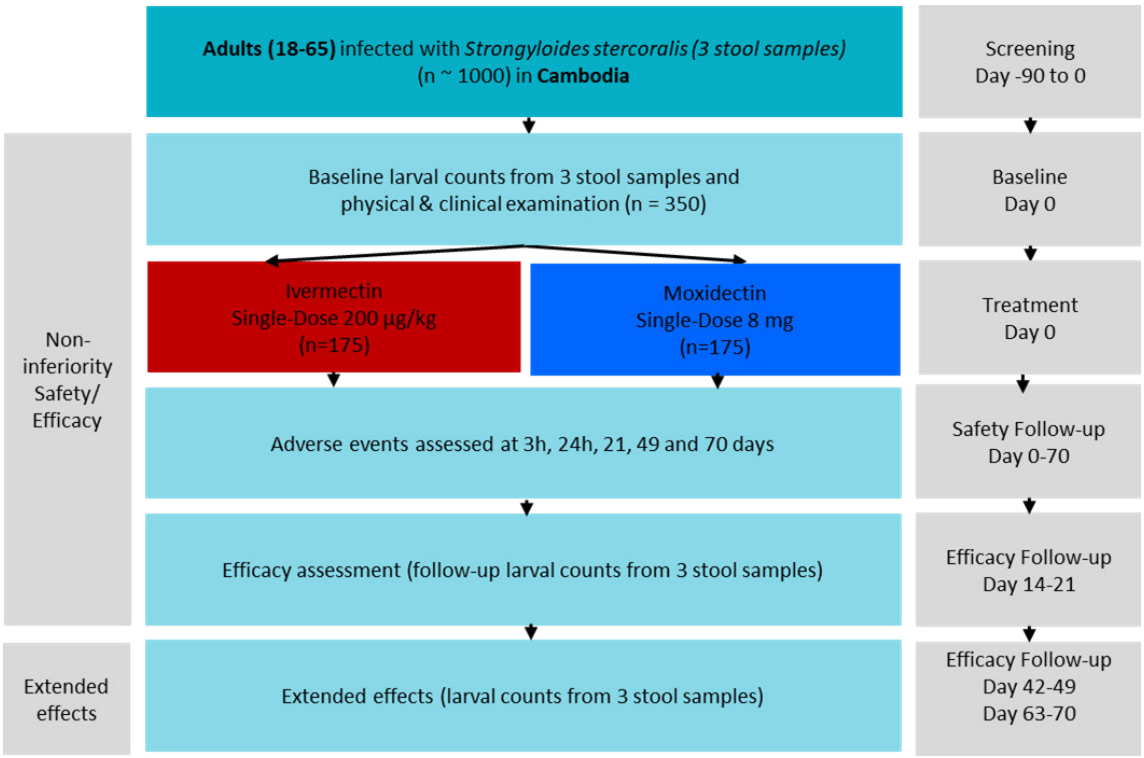

Figure 1. Design and timeline of the non-inferiority trial to be implemented. A loss to follow-up of 10% is assumed.

4.3.1. Diagnosis

At baseline, all participants will be asked to provide three stool samples. The stool samples will be collected until a total of approximately 400 *S. stercoralis*-infected adults are registered, which assumes a lost to follow-up of 10%. As diagnosing very low-intensity chronic infections remains a major challenge for quantitative and qualitative analysis for *S. stercoralis*, Baermann assays will be done in duplicates and the average over three stool samples will be taken for analysis [36, 37].

To this end, a quantitative Baermann funnel concentration technique will be used for the quantitative assessment of *S. stercoralis* infections [37-39] using stool samples from three different days. The stool samples will be warmed in a water bath to 36°C. A 5 g stool sample will be placed on gauze inserted into a glass funnel and covered with temperature 36°C water. Following two hours of artificial light exposure, the collected liquid will be centrifuged and the sediment prepared for analysis by microscope [40, 41].

Moreover, from the first two stool samples from each participant a duplicate Kato-Katz thick smear will be prepared to detect co-infections with any of the three major STHs, namely *A. lumbricoides*, *T. trichiura* and the hookworms as well as *Taenia ssp*. [42]. In case we identify positive *Taenia ssp.* cases stool samples will be used for the further development of new diagnostic tools.

The slides from the Baermann and Kato-Katz thick smears will be analyzed under a microscope by experienced technicians and a subsequent independent quality control of sample results (approximately 10%) will be conducted. *S. stercoralis* larvae will be counted quantitatively. Co-infections with STH eggs will be recorded qualitatively for the different species and assigned as egg positive or negative. Results are considered correct if the following tolerance margin is not exceeded: (i) No difference in presence/absence of each species separately for counts ≥1 egg/larvae, (ii) larvae counts are +/-10% larvae for counts ≤100 larvae or +/-20% for counts >100 larvae [43]. In case discrepancies above the tolerance margin are noted, 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. Infection intensity expressed as the arithmetic and geometric mean larvae count per gram of stool will be calculated. All microscopically analyzed Baermann samples as well as the Kato-Katz thick smears will be destroyed after passing the quality control.

The same sampling procedure and diagnostic approach will be applied at the defined follow-up time points.

4.3.2. Clinical examination

A clinical examination of the study participants assessing general health, anthropometric parameters including height and weight as well as frontal temperature using an frontal no-touch thermometer will precede the treatment. Each participant will be asked to provide a finger-prick blood sample for haemoglobin (Hb) levels, which will be detected using a HemoCue analyzer (Hb 301 system, Angelholm, Sweden). To avoid accidental treatment of pregnant women all female participants will be asked to provide a urine sample to be subjected to a pregnancy rapid diagnostic test at baseline. Women will be strongly advised to avoid becoming pregnant during the entire study period. All trial participants will further be asked about existing clinical symptoms before drug administration.

4.3.3. Adverse effects assessment

Participants will be kept for 3 hours after treatment administration to observe any possible acute adverse events (AEs) and re-assessment will be done at 24 hours 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, 42-49 and 63-70 days post-treatment, participants will again be interviewed for the assessment of adverse events. Symptoms arising within the time span of 14 days after treatment and the respective follow-up time points will be monitored actively by local health workers who will report incidences to the study team. Any symptoms will be recorded in the case report form (CRF) and immediate action will be pursued if indicated.

4.3.4. Assessment of efficacy after treatment

The efficacy of the treatment will be determined 14-21 days post-treatment by collecting another three stool samples. Stool samples will be microscopically examined for *S. stercoralis* applying each duplicate Baermann technique as well also for potential co-infection with *A. lumbricoides*, *T. trichiura*, hookworm and *Taenia ssp.* eggs using each duplicate Kato-Katz thick smears on the first two stool samples. The efficacy of the moxidectin and ivermectin will further be assessed 42-49 days after treatment and 63-70 days after treatment by duplicate Baermann technique.

Participants will be considered *S. stercoralis* cured if no larvae have been found in any of the stool samples. Infection is calculated as larvae per gram stool (LPG). LPG will be assessed by calculating the mean of the larvae counts from the corresponding multiple Baermann assays and adjusted to the previously weighted used amount of stool sample. At the end of the study (day 70) all participants remaining positive for *S. stercoralis* will be treated with ivermectin (200

µg/kg), the current standard drug against *S. stercoralis* [9]. Study participants positive for co-infection will be treated with the currently and locally standard treatment option.

4.3.5. Household Questionnaire

A household-based questionnaire will be administered to one member of each participating household to adjust for known influencing factors with regard to re-infection and infection intensity [30, 31] in the subsequent analysis and to identify risk factors for residual infections [44]. The questionnaire will assess information on socioeconomic characteristics (e.g condition and amenities), access to sanitation and water facilities (e.g. latrine, toilet, shower, water source) as well as hygiene behavior (e.g. defecation, hand washing, water use). The questionnaire is based on the core questions recommended by WHO and UNICEF.

4.3.7 Daily stool sampling

Larval excretion pattern is determined from 50-100 participants. Stool will be collected of these participants every day after treatment administration until day 28.

4.3.8 Genetic Profiling

From all *S. stercoralis* positive participants, the extracted larvae will be stored in 70% Ethanol after examination by Baermann at each analysis time point (baseline, follow-up 1, 2 and 3). Samples will be shipped to the investigating laboratory (La Trobe University) at room temperature.

4.4. Measure to minimize bias

Study participants eligible for treatment will be randomly assigned to one of the two treatment arms using a computer-generated stratified block randomization code. The random allocation sequence with varying random blocks of 4 and 6 will be provided by a statistician not involved in enrolment, treatment, and data collection. Separate sequences will be generated for three levels of baseline infection intensity (light ≤1 LPG, moderate >1-10 LPG and heavy >10 LPG). The codes will be held at the Swiss Tropical and Public Health Institute. A copy of this code will be kept in a sealed envelope by one of the co-investigators and will only be opened in emergency situations, determined by the principal investigator (PI) upon consultation with the co-investigators (co-PI). Allocation concealment will be maintained by masking the randomization sequence from the team member conducting the recruitment. Participants are blinded towards the study drugs (double-blinded).

Masking of the outcome assessor is ascertained in all treatment arms since the laboratory technicians determining the larvae counts and presence of egg for efficacy assessment will

have no knowledge of the participants assignment to treatment arm. The blinding will be maintained throughout the trial until data entry and processing are complete and the data have been verified. Following release of the final data, the randomization codes will be released.

4.5. Study duration and duration of participation

The trial will last a maximum of 26 weeks. The screening for the baseline will start 12 weeks prior to the treatment. Follow-up screening will take place 14-21, 42-49 and 63-70 days post-treatment and last for about one week. Schedules of visits are summarized below (Table 1).

4.6. Schedule of visits

Table 1. Schedule of visits

	Screening / Baseline / Treatment / Safety						Follow-up period		
	Day -90	Day -3 - 0	0 h		1-3 h	24 h	Day 14-21	Day 42-49	Day 63-70
Informed consent	X			Randomization and administration of treatment					
Diagnosis (stool exam) [a]	X						X	X	X
Baseline data [b]	X								
Questionnaire	X								
Medical history [c]		X							
Clinical examination [d]		X							
Physical examination [e]		X							
Randomization administration of treatment			X						
Capturing AEs [f]					X	X	X	X	X
Capturing SAE [f]					X	X	X	X	X

[a]) based on duplicate Baermann assays of three stool samples. Daily stool sample will take place in 50-100 adults between day 0 and day 28.
[b] date of birth, age, sex, height, weight, body temperature, pulse rate, blood pressure, Hb measurement, pregnancy test and recording of breastfeeding.
[c] information gained by asking specific questions concerning chronic disease and concomitant medications.
[d] investigation for signs of disease: head ache, abdominal pain, nausea, vomiting, diarrhea, itching, other symptoms.
[e] physical examination on ear, nose, throat, eyes, lungs, lymph nodes and skin.
[f] a standardized symptom questionnaire is used, that includes the recording of headache, abdominal pain, itching, nausea, vomiting, diarrhea, allergic reaction, others.

5. Selection of the trial participants

5.1. Recruitment

The study will be carried out in adults in areas endemic for *S. stercoralis* in Kampong Chhnang province, Cambodia.

The adult community members will be invited to participate in an open community information meeting to explain the purpose and procedures of the study, including potential benefits and risks. Potential participants will be encouraged to ask questions in an open discussion followed by this meeting.

Those adults interested in the study will be invited to complete the process of informed consent. See section 9.3 for details on obtaining informed consent. Only those participants who have written informed consent will be assessed for study eligibility criteria during screening procedures.

5.2. Inclusion criteria

1. Males and females aged 18-65 years infected with *S. stercoralis (*positive in at least one of the three provided stool samples or at least two of the sextuplicate Baermann assays (0.07 LPG in 10 g of stool).
2. Written informed consent signed by the participant him/herself. 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 thumbprint.
3. Agree to comply with the study procedures, including to be examined by a study physician before treatment and to provide three stool samples at the beginning (baseline) and three stool samples approximately two to three weeks after receiving treatment (follow-up 1). Further three stool samples are asked for at each long-term follow-up scheduled at 42-49 and 63-70 days-post-treatment.

5.3. Exclusion criteria

- Presence of acute or uncontrolled systemic illnesses (e.g. severe anemia, fever) as assessed by a medical doctor, upon initial clinical assessment.
- History of severe chronic disease or major systemic illnesses, e.g. severe anemia, severe chronic heart, liver or renal disease as asked by the medical doctor, upon initial clinical assessment.
- Treatment with anthelmintics (e.g. diethylcarbamazine [DEC], suramin, ivermectin, mebendazole or albendazole) within 4 weeks before study start.

- Attending other clinical trials during the study period.
- Pregnancy, lactating, and/or planning to become pregnant within the study period.
- Known allergy to study medications (i.e. moxidectin or ivermectin).
- Use of medication with known interaction on the study drug.

Participants who were diagnosed with a STH infection, but who were excluded from the study due to one or several of the above-mentioned exclusion criteria, including withdrawals, will be offered standard anthelminthic treatment (i.e. ivermectin at a single dose of 200 µg/kg).

5.4. Criteria for discontinuation of trial

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

1. withdraws from the study.
2. at the discretion of the PI or co-PI, if the participant is not compliant to the requirements of the protocol.

Discontinued participants will not be replaced. If, for any reason, a participant is discontinued from the study before the end of treatment evaluations, the planned procedures (AEs monitoring) will be conducted. Data obtained prior to the participant's withdrawal will be included in analysis. Data of withdrawn participants are fully anonymized once analysis is completed.

5.5. Treatment of participants

2 mg tablets of moxidectin and moxidectin placebo tables will be obtained from Medicines Development for Global Health (MDGH), Australia. Ivermectin (3 mg) will be purchased from Merck, Switzerland and matching ivermectin placebo tablets will be produced and a certificate of manufacture and analysis provided by the University of Basel. The body weight of each participant will be recorded to calculate and administer the correct dose of ivermectin (200 µg/kg). 8 mg (4 pills of moxidectin or moxidectin placebo) and the appropriate doses of weight-dependent ivermectin or its placebo will be calculated and administered to all participants. Each person (i.e. moxidectin 8 mg and ivermectin 200 µg/kg) will receive the maximum number of ivermectin tablets with regard to their weight category or the corresponding number of placebo tablets, and the four 2 mg moxidectin tablets or equal number of placebo tablets. The tablets will be handed out from the drug container according to the randomization list. The person conducting the recruitment and defining the order in which patients receive treatment will be masked to the randomization sequence so to warrant allocation concealment.

All drugs will be administered in the presence of the PI or co-PI and the physician, and ingestion confirmed. This will be recorded with the time and date of dosing. The tablets will as long as applicable be stored in the original package and at any time (except treatment day) be stored according to manufacture prescription, sealed and away from light. The PI 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.

After ingestion of the medication at every administration time point, the participants will be observed for 3 hours to ensure retention of the drug. Vomiting within 1 hour post-dosing will require re-dosing. The participants will not be allowed more than one repeated dose. No re-administration will be needed for participants vomiting after one hour. In case any SUSAR will be observed, any further treatment will be put on hold until the data has been reviewed and a decision taken within the entire study team whether the study can be continued or has to be stopped. On the treatment day, participants presenting a serious medical situation, as judged by the physician, will be kept at the hospital level under close supervision by a medical team. Also, in order to not break the surveillance of the undesirable effects of those whom we will allow to go back home at the end of the treatment day, security measures will be taken: (i) a card containing at least three phone numbers of the investigators and the study physician will be given to the participant him/herself. Participants will further be asked not to take any drugs other than those prescribed by the study medical team.

Treatment will be done community-based in local community buildings. Infrastructure as required for the study needs (i.e. tables, chairs, a cover from rain and sun) will be installed as necessary at the specific study days. Participants will receive a local breakfast two hours prior to treatment as well as lunch and snacks during the day once absorption of the drug is complete.

5.6. Concomitant therapy

All medications taken one month before and during the study period must until the last stool examination at day 63-70 (follow-up) 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 participants in case of fever, antiemetics to prevent nausea and vomiting and/or antibiotics to prevent or treat bacterial superinfection.

Medication(s)/treatment(s) NOT permitted during the trial

- No other active drugs against helminths are permitted during the trial. Participants receiving active anthelminthic concomitant medication during the trail will not be discontinued; however a case-specific assessment will be done at the time of data-analysis.

6. Assessment of safety

6.1. Adverse event definition

Few adverse events have been reported following moxidectin or ivermectin administration in STH-infected individuals. The most common AEs were abdominal cramps, headache, nausea, diarrhea, fever and vertigo [11, 12, 45, 46].

6.1.1. Types of adverse events

The term “adverse event” is defined as:

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

An AE can 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 sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
b) Any abnormality detected during physical examination.

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 drug” means that there is a reasonable possibility that the event may have been caused by the drug.

6.1.2. Severity grading

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

(*https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf*).

Grade Definition

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

6.1.3. Relatedness

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

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

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

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

6.1.4. Types of adverse events

Expected adverse event: Any adverse event possibly related to the study drug administration reported in the literature and/or on the drug package leaflets for moxidectin and/or ivermectin.

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

6.1.5. Serious adverse events

According to the ICH “Clinical Safety Data Management: Definitions and standards for expedited Reporting E2A” (https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf) a serious SAE includes any event (experience) or reaction in any untoward medical occurrence that at any dose:

1. is fatal, results in death;

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

A "severe" AE does not necessarily meet the criteria for a "serious" AE. Serious adverse events are reported from the first dose of study medication to 21 days post-treatment.

SAEs that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related (definitions will be used according to the WHO-UMC system; see: http://who-umc.org/Graphics/24734.pdf) to the study treatment or study participation will be recorded and reported immediately.

6.1.6. 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

The observation time for AE starts when the treatment is initiated. Participants will be kept for observation for at least 3 hours following each morning treatment for any acute AEs. During the reporting period, any unfavorable changes in the participant's condition will be recorded as adverse events, whether reported by the participant or observed by the investigator. In case of any abnormal finding, the local study physician will perform a full clinical examination and findings will be recorded. An emergency kit will be available on site to treat any medical conditions that warrant urgent medical intervention.

In addition, participants will also be interviewed by a health worker about the occurrence of AEs 24 hours after treatment.

For all AEs, sufficient information will be pursued and/or obtained so as to permit i) an adequate determination of the seriousness of the event (i.e. whether the event should be classified as a SAE); ii) an assessment of the casual relationship between the AE and the study treatments

(i.e. whether the event should be classified as an adverse drug reaction); and iii) an assessment of intensity of AEs by the study physician. 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 SAE, unexpected adverse drug reactions, or SUSARs must be reported as described in Section 6.3.

6.3. Reporting of serious adverse events

Any study-related unanticipated problem posing risk of harm to participants or others, and any type of serious adverse event including SUSAR, will be reported (within 24 hours after capturing the event and notification) to

Prof. Dr. Jennifer Keiser (principal investigator)
Swiss Tropical and Public Health Institute,
Tel.: +41 61 284-8218
Fax: +41 61 284-8105
E-mail: jennifer.keiser@swisstph.ch

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

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 the 'Ethik Kommission Nordwest- und Zentralschweiz' (EKNZ, Switzerland) and the National Ethic Committee for Health Research (NECHR) according to national rules. Fatal or life-threatening serious adverse events or SUSARs will be reported within 24 hours (between sponsor-investigator's knowledge about the event and notification) followed by a complete

report within seven additional calendar days. Other SAE and SUSARs that are not fatal or life-threatening will be filed as soon as possible but no later than 14 days after first knowledge by the sponsor-investigator.

7. Data management and data quality control

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

7.1. Source data

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

1. CRF: Primary data collection instrument for the study. It holds records of all clinical and physical examination data, treatment information and AEs. For every participant enrolled in the clinical trial, a corresponding CRF exists. All data requested on the CRF must be recorded, and investigators will review and approve each CRF for completion.
2. Census: 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 *Strongyloides* larvae counts and presence of STH eggs at all sample collection time points.

7.2. Data collection and documentation

The data collected and produced from this research project will fall into the following categories:

1. Larvae counts of *Strongyloides stercoralis*, presence of eggs of *Ascaris lumbricoides* and *Trichuris trichiura*, hookworms and *Taenia ssp.* found in participants' stool using either the Baermann technique or standard Kato-Katz microscopy.
2. Personal information such as name, age and gender of trial participants.

3. Baseline and clinical characteristics of the trial participants collected using the study's CRF such as weight, height, blood pressure, temperature, any abnormal medical condition or chronic disease.
4. Number and type of adverse events registered in the CRF and actively probed for 3 and 24 hours after treatment. The same data will further be collected during the collection of the three follow-up periods.
5. Socioeconomic data of each participant's household including behavioural characteristics based on the questionnaire.
6. Genetic profiling of *S. stercoralis* larvae in positive stool samples.

Data from categories 1-4, will be both paper-captured and directly into tablets using CommCare HQ (Digmagi, Inc., Cambridge, MA) or a comparable data-entry software. Data from category 5 will be captured by software only, data from category 6 by paper only. For all data, the software entries will represent the primary data source.

CommCare HQ is a routine data management system ensuring complete, consistent and reliable data entry. For quality assurance error, range and consistency checks will assessed. 15% of data will be controlled by a standard operating procedure; any discrepancies will be corrected by consulting the hard copy and corrected accordingly. If more than 1% of the double entered data display discrepancies, all data in categories 1-4 will be double entered by two independent people for quality assurance and verified as described.

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. Data analysis will be conducted with pseudonymized data and reporting of findings will be fully anonymized. In paper-based data collection, all missing data must be explained. All entries will be printed in blue ink. All corrections must be noted with the initials of the respective team member and dated. All categories will be merged into a single master file saved in .xlsx and .csv. Digital copies along with single databases and compiled masterfiles will be transferred to the Swiss TPH, Basel after a Material Transfer Agreement has been signed by both the Swiss TPH and National institute of Cambodia (see Appendix). All data is expected to not exceed 5 GB.
Essential infrastructure such as a locked room for safe storage of hardcopy data will be made available. Digital copies along with the databases will be transferred to the Swiss TPH. Data will then be analyzed as described in section 8.

7.3. Ethical, legal and security issues

Information about study participants will be kept confidential and managed accordingly. Screened participants will be listed in a confidential "participant screening log" and attributed a unique study number. Enrolled participants will be listed in a confidential "participant

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 participants. Confidentiality will be ensured throughout the entire research project. All databases will be password secured. None of the investigators declare to have any conflicts of interest.

7.4. Data storage and preservation

All samples will be destroyed after completion of the study. Paper-based and electronic source data and related material will be preserved for a minimum of 15 years to enable understanding of the study procedures, which allows the work to be assessed retrospectively and repeated if necessary. The study site 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 (Phnom Penh, Cambodia). 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 the PI and co-PI on a password-protected memory stick and/or 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. Definition of reference language – translation of study documents

- Protocol: Master document in English and Khmer, all further language versions are translations thereof.
- CRF: Master document in English and Khmer, all further language versions are translations thereof.
- ICF: Master document in English and Khmer, all further language versions are translations thereof.

8. Statistics

8.1. Definition of primary endpoint

Infection status of *S. stercoralis* assessed 14-21 days post-treatment by Baermann's method is the primary outcome.

8.2. Justification of number of trial participants

The main hypothesis of this trial is that an 8 mg dose of moxidectin is non-inferior against *S. stercoralis* compared to the standard of care therapy (ivermectin). We assume a similar true CR for moxidectin and ivermectin of 89% [16]. The sample size determination revealed, that we need 154 participants in each trial arm to demonstrate non-inferiority of moxidectin with a non-inferiority margin of 10%-points with 80 power at the 95% confidence interval (equivalent to the 97.5% lower confidence bound).

To account for an expected loss to follow-up of 10%, we target to enroll 175+175 = 350 participants.

8.3. Description of statistical methods

An available case analysis (full analysis set according to the intention to treat principle) will be performed, including all participants with any primary endpoint data. Supplementary, a per-protocol analysis will be conducted consisting of all participants who meet all inclusion and exclusion criteria, have no major protocol deviations and received the correct treatment. CRs will be calculated as the percentage of worm-positive adults at baseline who become worm-negative after treatment at the defined follow-up time points. Uncertainty estimates around the differences among CRs will be assessed using melded confidence intervals with mid-p correction as implemented in R's 'exact2x2' package.

LPG will be assessed by calculating the mean of the larvae counts from the Baermann assays (sextuplets for primary endpoint) per gram of stool. The LRR will be calculated (LRR = (1-(mean at follow-up/mean at baseline))*100). Bootstrap resampling method with 5,000 replicates will be used to estimate 95% confidence intervals (CIs) for LRRs and the difference between the LRRs.

Questionnaires on physical functioning and treatment satisfaction will be evaluated by creating summary scores by summing up and transforming the single question scores according to the following formula: [(actual raw score-lowest possible raw score)/(possible raw score range)]*100 [47].

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

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 (ICH-GCP E6 (R2)) and the current version of the Helsinki Declaration.

All protocol modifications must be documented in writing and implemented only with ethical approval. A protocol amendment can be initiated by any investigator. The investigator will provide the reasons for the proposed amendment in writing upon discussion with the Sponsor-Investigator. Any protocol amendment must be approved and signed by the Sponsor-investigator and must be submitted to the appropriate Independent Ethics Committee (IEC) for evaluation 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). Clinical trial insurance is set up with the FORTE INSURANCE (Policy Number: D/001/CPID/21/000002) in Cambodia.

9.3. Project management

The trial team will include the PI (Prof. Jennifer Keiser), a Co-PI (Dr. Rekol Huy in Cambodia), a Co-PI and physician (Dr. Virak Khieu in Cambodia), a Co-PI (Ms. Viviane Sprecher), a trial statistician (Dr. Jan Hattendorf), and laboratory technicians, health workers and nurses. Prof. Jennifer Keiser and Ms. Viviane Sprecher 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 Rekol Huy will be responsible for the administration of the Project. Dr. Virak Khieu has the main medical responsibility and is responsible for supervision of the lab- and field technicians, staff management, recruitment monitoring, supply of the material, contact with the local authorities and participating institutions.

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, GCP and GLP. 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 Cambodia. The study will be undertaken in accordance with the Declaration of Helsinki and good clinical practice (GCP E6 (R2)).

10.2. Evaluation of the risk-benefit ratio

Moxidectin is a well-known, FDA-approved drug against onchocerciasis and has little and mainly mild adverse events (headache, abdominal pain etc.). All community members enrolled in the study will benefit from a clinical examination and a treatment against STHs. All participants remaining positive for *S. stercoralis* will be treated with ivermectin (according to WHO recommendations) upon evaluation of the follow-up stool data. Participants still showing co-infection with hookworm, *A. lumbricoides*, *T. trichiura* or *Taenia ssp.* at follow-up assessment will be provided the current standard treatment.

10.3. Participant information and consent

Information sessions in the respective communities allowing for open exchange will be organized in every study locality where a screening, potentially also a prescreening, for identification of positive cases is to be conducted. The purpose and procedures, the benefits and risks of the study will be explained in order to make sure that all community members are at the same level in terms of information. All participants will be individually informed about benefits and risk associated to the trial. They will have sufficient time for reflection of their own participation. All eligible adults (≥18 years) will then be asked 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 sign or give a thumbprint.

Information sheets (ICS) are printed in Khmer and will additionally be verbally explained in the local languages during community meetings. To all participants a signed copy of the informed consent form will be given. Participation is voluntary and all participants 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. However, transport and meals will be covered and free treatment for all diagnosed worms will be provided.

10.4. Participant confidentiality

The obtained data will be handled strictly confidentially. Only members of the study team will have access to the data.
Screened patients will be listed in a confidential "participant screening log". Enrolled patients will be listed in a confidential "participant enrolment log" and attributed a unique study number; this document will constitute the only source to decode the pseudonymized data and will only be accessible to the local principal investigator. Data analysis will be conducted with pseudonymized data and reporting of findings will be fully anonymised; personal data will be coded for data analysis. No names will be published at any time, and published reports will not allow for identification of single participants. Confidentiality and anonymity will be ensured throughout the entire research project. All databases will be password secured. Participant-specific information may be provided to other appropriate medical personnel only with the participant's permission.
The investigators have all been trained in GCP. None of the investigators declare to have any conflicts of interest.

10.5. Participants requiring particular protection

This study will be carried out in adults, since *S. stercoralis* infection occurs most often in adults; hence this age group is at high risk of infection. Non-inferiority studies to the standard treatment options have not been conducted to date in this population. Our trial will provide more evidence and pave the further way for a safe and effective treatment of *Strongyloides* infections in adults and the whole community.

10.6. Other aspects

We will not include a placebo arm. Owing to the auto-infection cycle of *S. stercoralis* and due to the rather long follow-up periods, we prefer not to expose any adults to the risk of developing medical concerns. Considering all security measures (i.e. clinical and physical exams) set up for inclusion of trial participants in combination with the expected high true CR of roughly higher

than 90% for each treatment arm, we believe that a follow-up period of 70 days is not expected to cause any problem.

11. Quality control and quality assurance

11.1. Monitoring and auditing

We will work with a locally based monitor. He/she will conduct site visits to the investigational facilities for the purpose of monitoring the study. Details on scope and frequency of monitoring activities 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 preventive action plan will be requested and documented in response to any significant deviation. No sponsor-initiated audits are foreseen, but audits and inspections may be conducted by the local regulatory authorities or ethics committees and 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 no data and safety monitoring board will be established, since we work with well-known drugs. However, advisors will be informed regularly and the findings discussed.

12. Dissemination of results and publication

The final results of this study will be published in a scientific journal and presented at scientific conferences. The EU-Southeast Asia and the Adiuvare Foundation will be acknowledged as study funder. All results from this investigation are considered confidential and shall not be made available to any third part by any member of the investigating team before publication. A study report will be shared with the local ethics committees and the national regulatory authorities. After publication, study results will be made available to study participants.

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