Efficacy, safety and pharmacokinetics of ascending dosages of moxidectin alone and in comparison to ivermectin against *Strongyloides stercoralis* infection in adults: a randomized controlled trial

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Study Protocol

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Funding Agency	European Research Council (ERC), Fondazione Adiuvare		

1. General Information

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Dr.	Daniela Hofmann	Swiss Tropical and Public Health Institute	Postdoc	Co-investigator
Dr.	Jan Hattendorf	Swiss TPH	Group leader	Statistician

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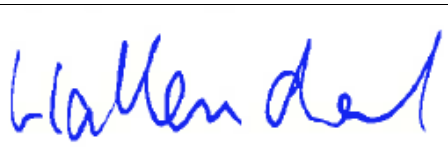
Signature		Date of Signature 01.07.2020
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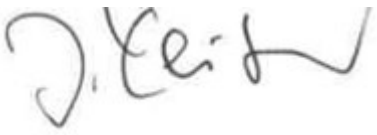
Signature		Date of Signature 01.07.2020
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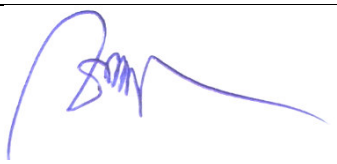
I have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and will complete the trial within the time designated. I will provide copies of the protocol and all pertinent information to all individuals responsible 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 01.07.2020
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IV. Synopsis

Study Title	Efficacy, safety and pharmacokinetics of ascending dosages of moxidectin alone and in comparison to ivermectin against *Strongyloides stercoralis* infection in adults: a randomized controlled trial
Study Type	Phase 2 trials – Phase 2a (trial A) & Phase 2b/3 (trial B)
Sample size	210 (trial A) and 350 (trial B) in two settings
Indication	*Strongyloidiasis stercoralis* infection (larvae in stool)
Investigational Product and Reference Treatment	Investigational product: moxidectin Reference treatment: ivermectin
Protocol Number, Date and Version	2, 01.07.2020, v2.2
Trial registration	Will be registered on (http://www.controlled-trials.com/)
Study Rationale	To provide evidence on: (A) Effective doses and safety of moxidectin in adults against infection with *S. stercoralis* in Laos (trial A: dose finding study). (B) Efficacy and safety of moxidectin compared to ivermectin in adults against infection with *S. stercoralis* in Laos and Cambodia (trial B: parallel group study).
Study Objectives	To determine the efficacy and safety of: a) seven ascending oral moxidectin dosages in adults infected with *S. stercoralis*, namely placebo, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg and to measure moxidectin disposition in adults using a microsampling device. b) the recommended dose moxidectin (i.e. the most promising dosage identified in trial A; 8 mg) in comparison to the standard treatment dose of ivermectin (200 µg/kg) in adults infected with *S. stercoralis.* Our **primary objective** is to determine the dose-response of moxidectin based on cure rates (CR) against *S. stercoralis* and to quantify the efficacy of the recommended dose to the standard treatment (ivermectin) in adults: a) in a dose finding study placebo, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg moxidectin b) in a parallel group trial

	8 mg moxidectin (absolute value depends on results of (A)), and 200 µg/kg ivermectin. The **secondary objectives** of the trial are: 1) to evaluate the safety and tolerability of the dose-dependent treatment regimes. 2) to evaluate the safety and tolerability of moxidectin compared to ivermectin. 3) to compare the larvae reduction rate (LRR) of the different treatment regimens against *S. stercoralis* (trial A and B). 4) trial A: to determine an exposure- (including C_{max}, AUC and t_{max}) -response correlation of moxidectin in adults. 5) trial A: to compare the exposure-response of moxidectin using venous and capillary blood. 6) to evaluate the cure rate of the different moxidectin treatment regimens against co-infection. 7) trial A: to determine the population PK parameters of the optimal dose of moxidectin in the treatment of *S. stercoralis.* 8) trial B: to relate socioeconomic characteristics (possession of indicator assets), access to sanitation, water facilities, and hygiene and environmental reservoirs behaviour to infection intensity
Study design	Single blinded, randomized controlled trial (trial A) (participants and lab technicians are blinded); double blinded randomized controlled non-inferiority trial (trial B)
Study product / intervention	Administration of a single oral dose of moxidectin or ivermectin
Comparator(s)	Matching placebo (trial A, B), Ivermectin (trial B)
Key inclusion / Exclusion criteria	**Inclusion:** Adults (≥ 18, <65 years) infected with *S. stercoralis*, absence of major systemic illnesses, written informed consent signed by individual **Exclusion:** Any abnormal medical conditions or chronic disease, negative diagnostic result for *S. stercoralis*, no written informed consent by individual. Pregnant women, lactating women or women planning to become pregnant within the next six months
Primary Endpoints	CR on *S. stercoralis*
Secondary Endpoints	LRR against *S. stercoralis*, safety and pharmacokinetic parameters in *S. stercoralis* infected populations

Exploratory Endpoints	Co-infection
Interim Analyses	None
Study Duration	8 weeks (trial A) / 8 weeks (trial B)
Schedule	08/2019 of first-participant in (planned) 08/2021 of last-participant out (planned)
Measurements & procedures	Three stool samples will be collected at baseline if possible on three consecutive days or otherwise within a total maximum of 6 days and analysed by a quantitative Baermann method (in duplicates) for *S. stercoralis* infection. Co-infection with *T. trichiura*, *A. lumbricoides* and hookworm infection will be identified using duplicate Kato-Katz thick smears on stool samples from two consecutive days. 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. The adults will also be interviewed before treatment, 3 and 24 hours as well as 28 days after treatment about the occurrence of AEs. The efficacy of the treatment will be determined 21-28 days post-treatment by collecting another three stool samples. All stool samples will be examined with duplicate Baermann assays and Kato-Katz thick smears and recorded quantitatively. A subsample of adults will further be sampled using finger pricking for micro sampling at 0, 2, 4, 8, 24, and 72 hours, 7 and 28 days post treatment to evaluate pharmacokinetic parameters (trial A). For validation of the analytical method the subsample of one study arm (8 mg, trial A) will undergo venous blood sampling in addition to finger pricking. To all participating households, a brief questionnaire will be administered assessing information on socioeconomic characteristics (possession of indicator assets) and access to sanitation, water facilities, and hygiene behaviour at first visit. Additionally, soil and water samples at different sites will be taken.
Statistical Analyses	An available case analysis (full analysis set according to the intention to treat principle) will be performed, including all subjects with primary end point data. Supplementary, a per-protocol analysis will be conducted. CRs will be calculated as the percentage of larvae-positive subjects at baseline who become larvae-negative after treatment. Larvae per gram (LPG) stool sample will be assessed by calculating the mean of the larvae counts from the three duplicate Baermann assays and divided by the mean weighted amount of these stool samples. The LRR will be calculated following: (LRR = (1-(mean at follow-up/mean 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 2,000 replicates will be used to calculate 95% confidence intervals (CIs) for LRRs. E_{max} models using the dose finding package of the statistical software environment R will be implemented to predict the dose-response curves in terms of CRs and LRRs. Trial A: E_{max} models using the Dose Finding package of the statistical software environment R will be implemented to predict the dose-response curves in terms of CRs and LRRs. Noncompartmental and nonlinear mixed-effects (NLME) modeling will be used to determine pharmacokinetic parameters. Trial B: The non-inferiority margin is set to 10%-points, i.e. If the lower bound of the 95% CI of the differences in cure rates is greater than -0.1 we conclude that moxidectin is non-inferior to ivermectin.
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 adults	This study will be carried out in adults, since an infection with *S. stercoralis* occurs most often in adults and the efficacy of different dosages of moxidectin and the non-inferiority to ivermectin in adults was not yet determined.
Recruitment procedure	(A) A dose-finding (DF) study on efficacy, safety and - for a subgroup of a total of 90 participants on PK parameters - on moxidectin will be conducted in 210 infected adults from rural communities situated in Nam Bak province in northern Laos (trial A: DF trial). (B) The parallel group study between moxidectin and ivermectin will be conducted as a non-inferiority trial with a margin of 10% in Laos and Cambodia recruiting 350 infected adult rural community members. The studies will be conducted in areas with moderate to high infection risk in Nam Bak province in northern Laos (prevalence: > %) of *S. stercoralis* identified from earlier studies and/or based on experience of the local collaborating teams.
Coverage of damages	Policy No: 021805872, Lao Viet
Storage of data and samples for future research aims	After the study has been completed all samples will be destroyed and case report forms 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.

V. Abbreviations

AE	Adverse event
AUC	Area under the curve
CI	Confidence interval
CR	Cure rate
CRF	Case report form
DALYs	Disability-adjusted life years
DBS	Dried blood spot
DF	Dose finding
DSMB	Data and safety monitoring board
EKNZ	Ethikkommission Nordwest- und Zentralschweiz
GCP	Good clinical practice
Hb	Hemoglobin
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
LPG	Larvae per gram
LRR	Larvae reduction rate
NLME	Nonlinear mixed-effects
NTD	Neglected tropical disease
PI	Principal investigator
PK	Pharmacokinetics
SAE	Serious adverse event
WHO	World Health Organization

2. Background information

Over the last decade, 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. NTD also includes soil-transmitted helminthiasis such as strongyloidiasis covered in this clinical study [1].

Strongyloides stercoralis is a soil-transmitted nematode found almost worldwide, though with largest prevalence in tropical and subtropical regions, as an example Lao PDR [2-4], and belongs to the most neglected infections among the NTDs.
Infectious larvae are found in humid soil that is contaminated with feces. 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 infections. Furthermore, *S. stercoralis* is known for its unique and threatening feature to cause systemic infection. Not surprisingly, without appropriate therapy, thus infections do not resolve and may persist for life. In case of immunodeficiency the infections are severe if not even life-threatening. However, most infections, chronic low-intensity infections, in particular, remain non-specific and might be expressed as suffering from malnutrition, physical and cognitive retardation, and reduced work performance [5]. *S. stercoralis* infections are typically most intense and debilitating in adults causing significant morbidity [6-8].

Today, chemotherapy combined with health education 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, which has a lower efficacy compared to ivermectin [9, 10]. Since drug resistance is a threat and the drug pressure is high 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 an excellent alternative. Moxidectin has been approved recently 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]. The drug 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 used successfully in veterinary medicine against ivermectin-resistant strains [14].

The clinical significant adverse advents of moxidectin are though very similar to those of ivermectin and a consequence of excessive concentration. The drug is typically used as a single oral dose (8 mg) in patients aged 12 years and older and evaluated as an extremely safe drug. 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. Laos and Cambodia are 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 (severe itching, bumps under the skin, blindness) 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 we do not see it recommended using moxidectin with pregnant female and pregnant patients 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. The risk of moxidectin in nursing infants is though unknown. Breastfeeding females will 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 its tolerability confirmed also in patients [15].

Yet, despite the attractive attributes of moxidectin and its promising potential in the treatment of *S. stercoralis* it remains off-label. First of all, the efficacy of the human formulation against *S. stercoralis* infections has not been assessed to date, neither has the optimal dosage been elucidated. A single dose of 36 mg moxidectin in healthy adults was the highest single dose tested to date that still represented a well-tolerated dose [13]. The 12 mg, therefore, selected as the highest dose in our study to elaborate a dose-response relationship for the use of moxidectin in *S. stercoralis* infections will not pose any health risk.

Second, to date pharmacokinetic studies of moxidectin have been conducted exclusively in a low number of healthy adults and consequently the pharmacodynamic behavior of moxidectin is completely unknown. [13, 16]. Yet, a PK characterization is central to understand the human body's response to a drug, especially in populations that physiologically differ from healthy adults. Physiological abnormalities like mal- or undernutrition and intestinal worms, such as *S. stercoralis*, can potentially affect the PK of a drug [17, 18]. Being minimal invasive, minimal painful, simple and rapidly performed, micro-blood sampling (e.g. the dried blood spot (DBS)) has developed into the method of choice for PK studies and will be also used in this study. Micro-blood sampling has been repeatedly proven to correlate well with the standard method that uses venous blood [19-22]. Micro blood sampling analysis has not been used to measure moxidectin blood levels and, therefore, requires a validation. For this purpose, a formal validation, using blood samples from two vascular sides, will be performed in parallel; supporting and confirming the linearity between venous and capillary blood also for moxidectin.

Last, it would be crucial to elucidate if moxidectin at an appropriate dose could serve as an alternative to ivermectin, which is to date one of the very few but the drug of choice against *S. stercoralis.*

In view of remaining knowledge gaps of the optimal doses of moxidectin against *S. stercoralis* as well as insufficient evidence on safety and efficacy parameters our study aims in a first step to thoroughly investigate the efficacy and safety of ascending doses of moxidectin (2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg versus placebo) against *S. stercoralis* infection, complemented by PK studies. Once the optimal dose of moxidectin has been identified in this phase 2a trial (trial A: DF study), we aim in a second study to compare the safety and efficacy of the single best dose of moxidectin to the standard dose of ivermectin in two phase 2b trial settings (trial B: parallel group study). This study will be complemented by assessing socioeconomic factors, household characteristics and behaviors, using a household questionnaire. Moreover, we will inform about potential environmental risk factors.

3. Trial objective and purpose

The primary study objectives are

(A) To determine the nature of the dose-response (efficacy in terms of cure rate) using oral moxidectin dosages: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg and placebo in a total of 210 adults infected with *S. stercoralis* (trial A: DF study).

(B) To determine if the efficacy in terms of cure rate of an oral single optimal dose of moxidectin (8 mg based on the outcome of (A)) is non-inferior to the standard dose of a single oral ivermectin application (200 µg/kg), in 350 infected adults in two settings. The non-inferiority margin is set to 10%-points (trial B: parallel group study).

The secondary study objectives are

1.) To compare the efficacy based on larvae reduction rates of ascending oral moxidectin dosages in a total of 210 adults infected with *S. stercoralis*.

2.) To determine safety & tolerability of ascending oral moxidectin dosages in a total of 210 adults infected with *S. stercoralis*.

3.) To comparatively assess the efficacy based on larvae reduction rates moxidectin versus ivermectin (200 µg/kg), the current drug of choice, against *S. stercoralis* in 350 adults infected with *S. stercoralis.*

4.) To determine safety & tolerability of moxidectin versus ivermectin (200 µg/kg), the current drug of choice, against *S. stercoralis* in 350 adults in two countries infected with *S. stercoralis.*

5.) To determine pharmacokinetic parameters in 10 adults infected with *S. stercoralis*, after oral moxidectin administration of 8 mg, using venous as well as capillary blood allowing the validation of the micro sampling analysis to measure moxidectin blood levels.

6.) To measure moxidectin deposition and determine exposure (including C_{max}, AUC and t_{max})-response correlation using a microsampling technology after oral moxidectin administration of 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg versus placebo in a total of 90 adults infected with *S. stercoralis*.

7.) To determine the population PK parameters of the optimal dose of moxidectin in the treatment of *S. stercoralis.*

4. Methodology

4.1. Primary and secondary endpoint

CR (i.e. conversion from being larvae positive pre-treatment to larvae negative post-treatment) is the primary endpoint. In addition, LRR and key PK parameters will be determined and safety & tolerability of treatment evaluated (secondary end points). CRs against co-infections are considered as exploratory endpoints.

4.2. Type of trial

Single blinded, randomized placebo-controlled, dose-ranging trial (trial A: DF study) (participants and lab technicians are blinded).
Double blinded, randomized, non-inferiority trial (trial B: parallel group study).
The PK sub-studies of trial A and trial B are single blinded.

4.3. Trial design

Two randomized-controlled trials will be conducted; a dose-ranging study (trial A) and a parallel group study (trial B), with seven and three treatment arms, respectively to be followed-up each over a 21-28 days period. The second comparative trial will be conducted as a non-inferior study with a non-inferiority margin of 10%-points.

(A) The DF study (Figure 1, top) is designed as a seven-armed trial including arms with ascending dose administration of moxidectin: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg and a placebo-arm.

(B) The parallel group study (Figure 1, bottom) is designed as a two-armed trial including one arm with a single drug administration of a standard dose of ivermectin (200 µg/kg) and one arm with a treatment of a single best dose of moxidectin (8 mg, according to the findings in (A)). The optimal dose of findings in (A) are evaluated as the dose that is high enough to demonstrate efficacy in the target population, yet low enough to minimize safety concerns and adverse events.

The two study cohorts are presented in the figures below:

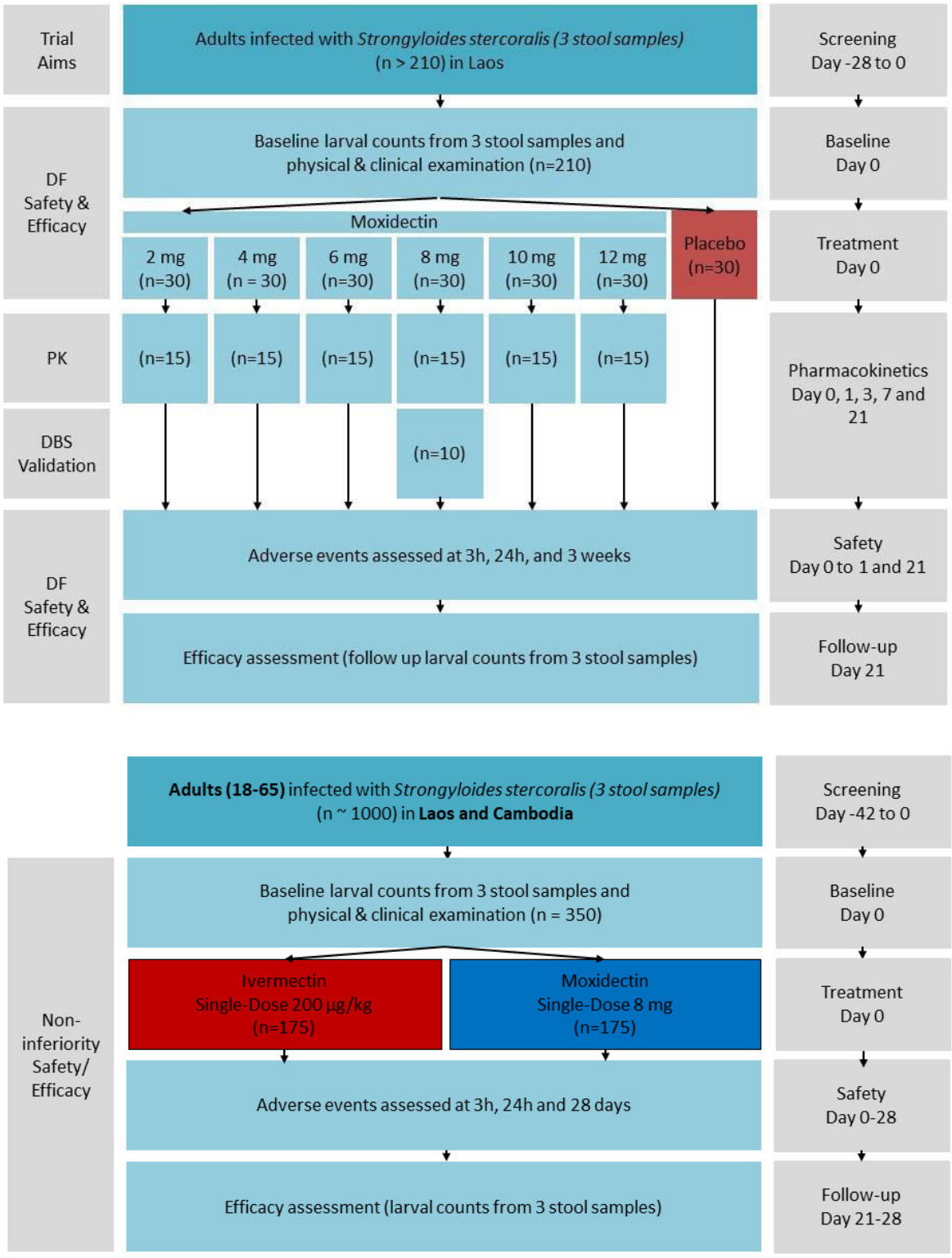

Figure 1. Design and timeline of the DF trial (top) and the parallel group trial (bottom) to be implemented. All sample sizes assume a drop-out of 10 %.

4.3.1. Baseline larval count

At baseline, all participants will be asked to provide three stool samples (if possible on three consecutive days or otherwise within a total maximum of 6 days) [23, 24]. The stool samples

will be collected until a total of 210 and 350 *S. stercoralis*-infected adults are registered (two out of three stool samples show more than 0.4 LPG (trial A) or 0.1 LPG (trial B), in 10 g of stool sampled per person and time point) in the two studies, respectively. As diagnosing very low-intensity chronic infections remains a major challenge for quantitative and qualitative analysis for *S. stercoralis* only low/moderate to high infection patients are included in trial A (LPG >0.4 on two out of three samples). This inclusion criterion has been shown to result in a diagnostic sensitivity of more than 97% to close to 100%. [24].

Firstly, a quantitative Baermann funnel concentration technique will be used for the quantitative assessment of *Strongyloides stercoralis* infections [24-26] using stool samples from three different (optimal consecutive) days. 5 g stool sample (the stool container with the sample will be weighted before and after the Baermann test was set up) will be placed on gauze inserted into a glass funnel and covered with preheated water to 36°C. Following two hours of artificial light exposure, the collected liquid will be centrifuged and the sediment prepared for analysis by microscope. Duplicate Baermann will be prepared from each stool sample [27, 28]. Secondly, from two stool samples from each participant a duplicate Kato-Katz thick smear will be prepared to detect co-infection with any of the three major soil-transmitted helminthic infections (STHs), namely *Ascaris lumbricoides*, *Trichuris trichiura* and the hookworms (*Necator americanus* and *Ancylostoma duodenale*) [29]. If additional coinfections are observed, they will be assessed likewise.

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 and eggs recorded for the different helminths species separately and qualitatively assigned as egg positive or negative. Results are considered correct if the following tolerance margin is not exceeded: (i) No difference in presence/absence *S. stercoralis*, (ii) egg/larvae counts are +/-10 eggs/larvae for counts ≤100 eggs/larvae or +/-20% for counts >100 eggs/larvae (for each species separately) [30]. In case discrepancies above the tolerance margin are noted in one or more slides, all 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 egg/larvae count per gram of stool will be calculated for each treatment arm. All microscopically analyzed Baermann samples as well as the Kato-Katz thick smears will be destroyed within one day (after passing the quality control).

4.3.2. Physical and clinical examination

At baseline, the medical history of *S. stercoralis*-infected participants in the study will be assessed with a clinical and physical examination carried out by the study clinician, who will assess weight, height, body temperature, pulse rate, blood pressure. Hemoglobin (Hb) levels will be detected using HemoCue to exclude severely anemic participants (below 80 g/l in adults according WHO) [31]. To avoid accidental treatment of pregnant women all female participants will be asked to provide a urine sample of at least 10 ml to be subjected to a pregnancy RDT. Women will be individually counselled that they should not become pregnant during the entire study period and will be interviewed if they are currently breastfeeding or planning to become pregnant. Any symptoms and abnormalities prior to treatment will be recorded on the case report form (CRF).

4.3.3. Adverse effects assessment

All participants will be kept for observation for at least 3 hours following each morning treatment for any acute adverse events and additionally will be interviewed and examined about existing and emerging clinical symptoms (i.e. headache, abdominal pain, itching, nausea, vomiting, diarrhea, body temperature, and allergic reaction) before treatment (baseline examination), 3 hours, 24 hours and 28 days after treatment (adverse effects assessment) to determine the occurrence of AE (see chapter 6.2). Any symptoms will be recorded in the CRF and immediate action will be perused (see chapter 6).

4.3.4. Assessment of efficacy after treatment

The efficacy of the treatment will be determined 28 days post-treatment by collecting another three stool samples, which will be microscopically examined for *S. stercoralis* applying each duplicate Baermann technique as well as for potential co-infection with *A. lumbricoides*, *T. trichiura* and hookworm eggs using each duplicate Kato-Katz thick smears on two stool samples.

Participants will be considered *S. stercoralis* cured if no larvae have been found in any of the stool samples. Infection was calculated as larvae per gram stool. LPG will be assessed by calculating the mean of the larvae counts from the three duplicate Baermann assays and adjusted to the previously weighted used amount of stool sample. At the end of the study (day 21) all participants remaining positive for *S. stercoralis* will be treated with ivermectin (200 µg/kg), the current standard drug against *S. stercoralis* [9].

4.3.5. Pharmacokinetic studies

Exposure-response correlation studies will be performed in a maximum of 15 participants per treatment arm (90 patients in total) (trial A: DF study). Since moxidectin is known to be better

absorbed in humans after a high-fat meal was consumed participants will receive a local high-fat breakfast prior to treatment [16]. Upon oral intake moxidectin levels in blood will be quantified with time using a micro sampling device. Therefore, capillary blood will be taken 0, 2, 4, 8, 24, and 72 hours, 7 and 28 days post-dosing (trial A). Micro sampling presents as one of the simplest, safest and least invasive study protocols. In our lab different blood micro-sampling techniques, including dried blood spots (DBS) and Mitra®, are currently under investigation to quantify moxidectin extracted in human blood samples. Following method development according to the U.S. FDA guidelines, the best protocol will be selected for the pharmacokinetic studies (i.e. DBS or Mitra®).

As yet the micro-blood sampling analysis has not been used to measure moxidectin blood levels in *S. stercoralis*, a formal validation will be performed next to the measurement of the PK values. For this purpose an additional blood sample will be taken from the venous side to demonstrate that the capillary and venous blood correlate satisfactory or to calculate the conversion coefficient. Venous blood will be withdrawn by cannulation from the same 10 adults of one treatment arm (8 mg) at identical time points post-dosing (trial A) [13, 16, 32].
In more detail, capillary blood (± 0.1 ml) will be collected by middle or ring finger tip puncture using a finger pricker (e.g. Accu-chek Softclix Pro®, Roche). Sampling will be conducted at the specified time points in doublets. A few drops of blood will be transferred at each time point on filter paper (Whatman) or on Mitra® sticks and dried for approximately 1 hour. The dried blood spot cards or Mitra® will be transported to Basel and stored properly until analysis. Moxidectin will be quantified using the validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Drug concentrations will be calculated by interpolation from a calibration curve with a foreseen limit of quantification of approximately 1-5 ng/ml. Quality control samples will be included in the study and its measured concentrations used to determine between-run and overall precision and accuracy of the analysis.

Venous blood (± 4 mL) will be collected in EDTA covered Vacutainer® tubes through an i.v. catheter placed in an antecubital arm vein. The indwelling catheter will be inserted in the arm not earlier than 1 hour before the beginning of the blood sampling. For the purpose of keeping the catheter patent, 0.9% sodium chloride (NaCl) will be slowly infused i.v. (1 drop per 2-3 seconds). Dilution artifacts will be avoided by interrupting the i.v. 0.9% NaCl drip prior to collection of the blood sample. In addition, approximately 0.5 ml of blood will be drawn through the catheter and wasted. Directly after the collection of the required blood volume (4 ml), the Vacutainer® tubes will be slowly tilted backwards and forwards (no shaking) to solve the anti-coagulant. 1 ml of blood will be transferred in a labeled tube, within 30 minutes post sampling. The remaining blood in the Vacutainer® will be centrifuged at about 3000 rpm for 10 min and

4°C to obtain plasma, which will be pipetted in another labeled polypropylene tube. The plasma and blood tubes will be kept in an upright position at -20 °C until analysis. The concrete time points of withdrawal of each blood sample will be entered in the form.

4.3.6. Questionnaire

A household-based questionnaire will be administered to one member of each participating household to adjust for known influencing factors with regard to reinfection and infection intensity [33, 34] in the subsequent analysis and to identify risk factors for residual infections [35]. The questionnaire will include assessment of / questions about information on socioeconomic characteristics (e.g structure, 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. To assess environmental risk factors, soil and water samples will be taken at specific sites in the village and analyzed microscopically.

4.4. Measure to minimize bias

Study participants eligible for treatment will be randomly assigned to one of the seven treatment arms (trial A: DF study) or to one of the two treatment arms (trial B: parallel group study) using a computer-generated stratified by 3 levels of baseline infection intensity (light ≥0.4 (trial A) or 0.1 (trial B) – 1 LPG, moderate >1-10 LPG and heavy >10 LPG), block randomization code. The random allocation sequence with varying random blocks of 7 or 14 (trial A) and 2 or 4 (trial B) will be provided by a statistician not involved in enrolment, treatment, and data collection. Stratification will guarantee similar proportion of participants with different infection intensities in all treatment arms. The number of light vs moderate vs. heavy infections, however, are not expected to be equal in each arm, depending on the distribution of infection intensity in the recruited cohort. The codes will be held in a locked cabinet 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 (will only be opened in emergency situations, determined by the principal investigator upon consultation with the co-investigators). 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.

In previous studies [36] we have observed moderate cure and larvae reduction rates in placebo treated children which are in most cases likely due to the imperfect sensitivity of anthelminthic diagnostics. Participants treated with placebo will be treated at follow up (4 post treatment) with ivermectin (200 µg/kg). This treatment delay does not cause noteworthy harm.

4.5. Study duration and duration of subject participation

The trial will last a maximum of 2 months, each (trial A and B). The screening for the baseline will start four weeks prior to the treatment. Follow up screening will take place 3-4 weeks post-treatment. Schedules of visits are summarized below (Table 1).

4.6. Schedule of visits

Table 1. Schedule of visits of DF (trial A) and parallel group (trial B) study.

	Screening /						Follow up
Time point	Day -28	Day -1-3	0 h	Randomization and administration of treatment	3 h	24 h	Day 28
Informed consent	X						
Diagnosis (stool examination) [(a)]	X						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
Capturing SAE [(f)]					X	X	X

[(a)] on three stool samples duplicate Baermann assays and on two stool samples duplicate Kato-Katz thick smears.
[(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 medication.
[(d)] investigation for signs of disease: head ache, abdominal pain, nausea, vomiting, diarrhea, itching, other symptoms.
[(e)] 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
[(g)] only in trial B

5. Selection of the trial subjects

5.1. Recruitment

The studies will be carried out in adults in areas endemic for *S. stercoralis* in Laos and Cambodia.

The adult community members will be invited to participate in an 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 forum.
Those adults who are 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 of age 18 – 65 infected with *S. stercoralis (*positive by at least two Baermann assays of two different days and infection intensities of at least 0.1 LPG in the two stool samples (5g stool / Baermann assay).
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 to give a thumb print.
3. Agree to comply with the study procedures, including to be examined by a study physician at the beginning of the study and to provide three stool samples at the beginning (baseline) and three stool samples approximately four weeks after treatment (follow-up).

Exclusion criteria

1. Presence of acute or uncontrolled systemic illnesses (e.g. severe anemia) as assessed by a medical doctor, upon initial clinical assessment.
2. 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.
3. Prior treatment with anthelmintics (eg, diethylcarbamazine [DEC], suramin, ivermectin, mebendazole or albendazole) within 4 weeks before planned test article administration.
4. Attending other clinical trials during the study.
5. Positive pregnancy test, lactating women and/or women planning to become pregnant within the next 6 months.

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. Participants suffering from clinical malaria (fever plus positive diagnostic test) will be treated according to national guidelines.

5.3. Criteria for discontinuation of trial

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

1. withdraws from the study (this can happen anytime as participation is voluntary and there are no further obligations once an adults withdraws).
2. at the discretion of the principal investigator, if the participant is not compliant to the requirements of the protocol.

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

5.4. Treatment of subjects

2 mg tablets of moxidectin will be obtained from Medicines Development for Global Health (MDGH), Australia. Ivermectin (3 mg) will be purchased from Merck, Switzerland. Matching placebo tablets (moxidectin and ivermectin) will be obtained from the Medicines Development for Global Health (moxidectin) and produced and a certificate of manufacture and analysis provided by the University of Basel (ivermectin). The appropriate doses will be calculated and the correct amount of moxidectin and placebo (trial A) and moxidectin, moxidecin placebo or ivermectin or ivermectin placebo tablets (trial B) will be administered to all participants. Due to blinding the tablets will be repacked into neutral separate opaque plastic bags each containing the adequate dose of moxidectin tablets and/or placebo tablets (trial A). In trial B, the tablets will be handed out from the drug container according to the randomization list. Each person will receive (i) either 4 moxidectin or 4 moxidecin placebo tablets and (ii) the number of ivermectin tablets with regard to their weight category or the corresponding number of ivermectin placebo tablets. 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 principal investigator(s) or co-investigator(s) 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.

Treatment and blood sampling (capillary blood sampling for a total of 90 participants, in trial A and venous blood sampling for 10 patients (trial A)) will be done community-based in local temples, that are quiet and spacious locations, where people like to gather and organize meetings. Infrastructure as required for the study needs (i.e tables, chairs, a fridge, a cover from rain and sun) will be installed as necessary at the specific study days. Opportunities

(approximately three daybeds) will be provided to comfortably withdraw the venous blood (4 samples on day 1 and 4 samples within the next 28 days) and to provide a possibility to lie down in case of an arising unwell feeling. Participants will receive a breakfast two hours prior to treatment as well as lunch during the day once absorption of the drug is complete.

On each treatment day a subgroup of participants will be treated with the different dosages. All drugs will be administered in the presence of the investigator(s) or co-investigator(s) and the physician, and ingestion confirmed. This will be recorded with the time and date of closing. Subjects will be asked not to take any drugs other than those prescribed by the study medical team. After ingestion of the medication, the subjects will be observed for 3 hours to ensure retention of the drug. Vomiting 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. In case any SAE will be observed, the study 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 of the project will be kept at the hospital level under close supervision by the medical team. Also, in order not to 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 himself.
We will be working with adults in rural areas. Participants who are involved in agricultural activities and migrating between locations will be provided with phone numbers so to follow them up with the help of health workers in case AEs occur.

5.5. Concomitant therapy

All medications taken one month before and during the study period must until the last stool examination at day 28 (trial A) post treatment (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 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

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, 36, 37].

The observation time for AE starts when the treatment is initiated. Subjects will be kept for observation for at least 3 hours following treatment for any acute AEs. 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 3, 24 hours, 28 days after treatment about the occurrence of AEs.
Information on all AE (incidence, onset, cessation, duration, intensity, frequency, 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).

6.1.1. Types of adverse events

The term “adverse event” is defined as:
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 can therefore be:

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.

The medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial will not be defined as AEs but as well be considered baseline medical conditions.
These data will be recorded on the appropriate CRFs, 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.

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 adverse events
2:	moderate adverse events.
3:	severe adverse events.
4:	life threatening or disabling adverse events.
5:	death related to adverse events.

The observation time for adverse events starts when the treatment is initiated and continues until 28 days post-treatment. For the purpose of this trial, disease progression and relapse will be considered as treatment failure, not as an AE.

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: Risks or events reported in the literature for moxidectin and/or ivermectin.

Unexpected adverse event: An unexpected event is any AE that is not identified in nature, severity, or frequency in the scientific literature.

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 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. 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 subject 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

Patients 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 subject's condition will be recorded as adverse events, whether reported by the subject or observed by the investigator. In case of any abnormal finding, the local study physician will perform a full clinical examination and findings will be recorded. An emergency kit will be available on site to treat any medical conditions that warrant urgent medical intervention.
In addition, patients will be also interviewed by a nurse and/or a physician about the occurrence of AEs 24 hours after treatment.
Information on all AEs (onset, duration, intensity, seriousness and causality) will be immediately entered in the appropriate AE module of the CRF which is considered as a source document. 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.

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 subjects or others, and any type of serious adverse event, will be reported (within 24h between site's knowledge about 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-investigator 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 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 serious adverse event reporting will be included in the trial-specific SAE form. Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant medications).

6.4. Safety reporting to Health Authorities and 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 ethic committee of Lao PDR 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 7 additional calendar days. Other serious adverse events 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. Statistics

7.1. Definition of primary endpoint

Cure rate is the primary outcome measure of our study.

7.2. Justification of number of trial subject

(A) *DF study*: Since it is already known that moxidectin acts on *S. stercoralis* and the existence of a drug effect is known, the main aim of the study is the elucidation of the nature of the dose–response relationship. Computer simulations showed that with 30 adults enrolled in each of the 7 study arms (0, 2, 4, 6, 8, 10, 12 mg) the dose response prediction model had a median precision (one half length of the 95%-confidence intervals) of 9%-points assuming associated true cure rates of 2.5%, 30%, 55%, 75% and 85%,

90%, 95% and a loss to follow up of 10%. The sample size is also in line with the recommendations from *Klingenberg et al. 2009* [38].

DF study - PK sampling: The suggested sample size of 15 participants per study arm is sufficiently high to determine the key PK parameters, considering that PK variability is low. A low PK variability is a reasonable assumption when dealing with adults.

(B) *Non-inferiority moxidectin versus ivermectin*: 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 CRs for moxidectin and ivermectin of 89% [15]. 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.

7.3. Description of statistical methods

An available case analysis (full analysis set according to the intention to treat principle) will be performed, including all subjects with primary end point data. Supplementary, a per-protocol analysis will be conducted. CRs will be calculated as the percentage of worm-positive adults at baseline who become worm-negative after treatment. LPG will be assessed by calculating the mean of the larvae counts from the three duplicate Baermann assays and relate this value to the mean weighted amount of stool sample. The LRR will be calculated (LRR = (1-(mean at follow-up/mean at baseline))*100).

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

Trial A: E_{max} models using the Dose Finding package of the statistical software environment R will be implemented to predict the dose-response curves in terms of CRs and LRRs.
Noncompartmental and nonlinear mixed-effects (NLME) modeling will be used to determine pharmacokinetic parameters.

On the basis of the LC-MS/MS measurements, the following PK parameters for plasma, whole blood and capillary blood will be calculated:

- 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. AUC and $t_{1/2}$ will calculated with the software WinNonlin (Version 5.2, Pharsight Corporation, USA) using compartmental analysis. The elimination half-life will be estimated by the equation: $t_{1/2} = \ln 2/\lambda$, where λ will be determined by performing a regression of the natural logarithm of the concentration values during the elimination period.

Trial B: The non-inferiority margin is set to 10%-points, i.e. if the lower bound of the 95% CI of the differences in cure rates is greater than -0.1 we conclude that moxidectin is non-inferior to ivermectin. The 95% confidence interval of the differences in CRs will be estimated using the standard formula:

$CI = (CR_{mox} - CR_{iver}) +/- Z_{a/2} * \sqrt{(SE_{mox}^2 + SE_{iver}^2)}$.

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 [39].

8. Duties of the investigator

8.1. 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 either the sponsor-investigator or any investigator. The investigator will provide the reasons for the proposed amendment in writing and will discuss 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 subjects, or when the change involves only logistical or administrative aspects of the trial, e.g. change of telephone number(s).

8.2. Damage coverage

A general liability insurance of the Swiss TPH is in place (Winterthur Police Nr. 4746321). Clinical trial compensation insurance is set up with the LAO-VIET insurance company (Policy 021805872). Another policy will be issue in Cambodia.

8.3. Project management

The trial team will include the PI (Prof. Jennifer Keiser), a co-investigator and physician (Dr. Somphou Sayasonein Laos, Dr. Virak Khieu in Cambodia), a co-investigator (Dr. Daniela Hofmann), a trial statistician (Dr. Jan Hattendorf) and laboratory technicians. Prof. Jennifer Keiser, Dr. Somphou Sayasone, Dr. Daniela Hofmann 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. Somphou Sayasone 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 to 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 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.

9. Ethical considerations

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

9.2. 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 participating subjects remaining positive for *S. stercoralis* will be treated with ivermectin (according to WHO recommendations).

9.3. Subject information and consent

Community meetings allowing for open exchange will be organized in every study locality where 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, <66) will be asked to sign a written informed consent sheet. They will have sufficient time for reflection of their own participation. They 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 to give a thumb print.

Information sheets are printed in English Lao and Khmer and will additionally be verbally translated into 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 of all diagnosed worms will be provided.

9.4. Subject 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 “subject screening log”. Enrolled patients will be listed in a confidential “subject 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 pseudonymised 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 subjects. Confidentiality and anonymity will be ensured

throughout the entire research project. All databases will be password secured. Subject-specific information may be provided to other appropriate medical personnel only with the subject's permission.
The investigators have all been trained in GCP. None of the investigators declare to have any conflicts of interest.

9.5. Subjects requiring particular protection

This study will be carried out in adults, since *S. stercoralis* infection occurs often in adults; hence this age group is at high risk of infection. Pharmacokinetic, dose-finding and non-inferiority studies 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.

9.6. Other aspects

We will include one group of adults treated with placebo in each of the arms. However, this group will be treated with a standard treatment of a single dose ivermectin (200 µg/kg) at the end of the study (already 3-4 weeks later); hence this does not cause any medical concern. Considering all security measures (clinical, physical and biochemical exams) set up for inclusion of trial participants, any person showing an unfavorable medical condition will not be included in the trial. Hence we believe that a treatment delay of 3-4 weeks is not expected to cause any problem. Of note, populations at risk are in general treated only in yearly intervals to reduce morbidity from chronic infections within MDA campaigns of national control programs.

10. Data management

The investigators are responsible for an adequate data quality. Prior to the initiation of the study, a short 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, CRF completion, specimen collection and diagnostic methods.

10.1. Data collection

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

1. Eggs/Larvae counts of hookworm, *Ascaris lumbricoides* and *Trichuris trichiura* and *S. stercoralis* found in participants' stool, soil or water samples using either the Kato-Katz or the Baermann technique before (baseline; stool, soil, water) and after (follow-up; stool) treatment.
2. Personal information such as name, age and gender of trial participants.
3. Anthropometric 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 be collected during the collection of the follow-up, 28 days after treatment.
5. Pharmacokinetic parameters such as C_{max}, AUC, or t_{max} analyzed from capillary or venous blood sampling at 0, 2, 4, 8, 24, and 72 hours, 7 and 28 days post dosing or in between 0 and 28 days post dosing.
6. Questionnaire: Record of the socioeconomic data of each participant's household

Data from categories 1-5 will be both paper-captured and directly into tablets using CommCare HQ (Digmagi, Inc., Cambridge, MA). 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 standard operating procedure, any discrepancies will be corrected by consulting the hard copy. If more than 1% of the double entered data display discrepancies, all data in categories 2-4 will be double entered by two independent people for quality assurance and verified as described.

Data entered into CommCare HQ databases will only be accessible to authorized personnel directly involved with the study by use of a password. It will directly be saved on the personal, password-protected laptop of one of the Co-PIs and uploaded to a server hosted at Swiss TPH, Basel. Data in category 1-4 will be saved both in .xlsx and .csv.

Data from categories 6 will be captured by software only. All categories will be merged into a single master filed saved in .xlsx and .csv. Data will then be analyzed as described in section 7. PK parameters (category 5) derived from analyzing micro blood and whole blood samples will be merged and saved as a .xlsx, .txt or/ and .m file.

10.2. Data handling and definition of source data - data entered directly in the Case Report Form

Source Data are the clinical findings and observations, laboratory data maintained at the study site. Source data are contained in source documents. Local authorities are allowed to access

the source data. Data will be entered directly into the case report forms. The CRF is considered as a ***source document***.

A CRF will be completed for each subject enrolled into the clinical study. The investigators will review, and approve each completed CRF. The study CRF is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked “N/D” will be entered. If the item is not applicable to the individual case “N/A” will be written. All entries will be printed in black ink. All corrections must be initialed and dated.

The study site (National institute of Laos) will retain a copy of the CRF to ensure that local collaborators can provide access to the ***source documents*** to a monitor, auditor, or regulatory agency while a copy of the CRF will be taken to Swiss TPH.
Digital copies along with the databases will be transferred to the Swiss TPH after a Material Transfer Agreement has been signed by both the Swiss TPH and National institute of Laos (see Appendix). All data is expected to not exceed 5 GB.

10.3. Definition of reference language – translation of study documents

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

10.4. Storage and preservation

After the study has been completed all samples will be destroyed. Data and related material will be preserved for a minimum of 15 years to enable understanding of what was done, how and why, which allow the work to be assessed retrospectively and repeated if necessary. Essential infrastructure such as lockable cabinets for safe storage of hardcopy data will be made available. Storage and backup will be in three places: personal password-protected laptops of Jennifer Keiser, Daniela Hofmann, Virak Khieu and Somphou Sayasone, Swiss TPH shared server and SWITCHdrive (a cloud storage supported by University of Basel). To the shared server and SWITCH drive only the above mentioned study team has access. Electronic data files and archiving conditions will be made strictly confidential by password protection.

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 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 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 in a small sample size and using a single dose treatment. 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 European Research Council 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.

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Appendix 1

Material Transfer Agreement
Between

National Institute of Public Health, Vientiane, Laos
(Hereinafter referred to as PROVIDER)

And

Swiss Tropical and Public Health Institute
Socinstrasse 57, CH-4051 Basel
(Hereinafter referred to as RECIPIENT)

Preamble

PROVIDER's has sampled Original Material in the course of or academic research.

RECIPIENT wishes to conduct non-commercial research with MATERIAL.

PROVIDER is willing to provide the Original Material to RECIPIENT under the following terms and conditions:

1. Definitions:

"Recipient's Scientist" is Prof. Jennifer Keiser

„Original Material"shall mean the following biological material and Data (s):

- Blood samples of PK participants
- CRF data of study participants

"MATERIAL" shall mean Original Material and Progeny and Unmodified Derivatives thereof as well as any accompanying information.

"Progeny" shall mean unmodified descendant from the MATERIAL, such as cell from cell.

"Unmodified Derivatives" shall mean substances created by RECIPIENT which constitute an unmodified functional subunit or product expressed by the Original Material.

"Modifications" shall mean substances created by RECIPIENT which contain/incorporate the MATERIAL.

2. The MATERIAL is, regarding the inherent intellectual property rights, the property of PROVIDER and is to be used by RECIPIENT solely for non-commercial research purposes at RECIPIENT's institution and only under the direction of the Recipient's Scientist. The research to be conducted by Recipient's Scientist is restricted to the project described in the study protocol.
3. The Recipient's Scientist agrees not to transfer the MATERIAL to anyone who does not work under his or her direct supervision at RECIPIENT's institution without the prior written consent of PROVIDER.
4. (a) PROVIDER retains ownership of the MATERIAL, including any MATERIAL contained or incorporated in Modifications.

(b) RECIPIENT retains ownership of: (i) Modifications (except that, PROVIDER retains ownership rights to the MATERIAL included therein) and (ii) those substances created through the use of the MATERIAL or Modifications, but which are not Progeny, Unmodified Derivatives or Modifications.

5. Except as expressly provided in this Agreement, no rights are provided to RECIPIENT under any patents, patent applications, trade secrets or other proprietary rights of PROVIDER. In particular, no rights are provided to use the MATERIAL or Modifications and any related patents of PROVIDER for profit making or commercial purposes, such as sale of the MATERIAL or Modifications, use in manufacturing, provision of a service to a third party in exchange for consideration, or use in research or consulting for a for profit entity under which that entity obtains rights to research results.

6. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS.

7. Except to the extent prohibited by law, RECIPIENT assumes all liability for damages that may arise from its use, storage or disposal of the MATERIAL. PROVIDER will not be liable to RECIPIENT for any loss, claim or demand made by RECIPIENT, or made against RECIPIENT by any other party, due to or arising from the use of the MATERIAL by RECIPIENT, except when caused by the gross negligence or willful misconduct of PROVIDER.

8. Recipient's Scientist agrees to provide appropriate acknowledgment of the source of the MATERIAL in all publications and agrees to send PROVIDER a copy of any such publications.

9. RECIPIENT acknowledges that the MATERIAL is human material which may underlay specific legislations of privacy protection. RECIPIENT agrees (i) to use the MATERIAL in compliance with all applicable statutes and regulations including, for example, all applicable data privacy laws, (ii) to use the MATERIAL in accordance with patient consent, (iii) to secure that if he is informed by PROVIDER that a patient withdraws his or her consent to use his or her material, any such MATERIAL which is in RECIPIENT’s possession is immediately destroyed and not longer used.

11. The Research using the MATERIAL shall last not longer than 10 years, unless the Agreement is formally extended. It is the responsibility of the RECIPIENT to seek such a prolongation. In the event RECIPIENT is not using and does not intend to use the MATERIAL or as soon as the Research will be concluded or this Agreement will expire or be terminated for whatever reason, the RECIPIENT is obliged to return to PROVIDER, if possible, or to destroy with required care, all MATERIAL.

12. The MATERIAL is provided without a fee.

13. The effective date of this Agreement is the date of the last required signature obtained.

14. This Agreement shall be construed and interpreted in accordance with the laws of Switzerland. Place of jurisdiction shall be Basel (Switzerland).

In Witness Whereof, the parties hereto have caused this Agreement to be executed on the dates set forth below by their duly authorized representatives.

For PROVIDER

Date: _____

By: _____ _____
Dr. MD Somphou Sayasone *(Signature)*
National Institute of Public Health, Vientiane, Laos

For RECIPIENT

Date: _____

By: _____ _____
Prof. Jennifer Keiser *(Signature)*

Date: _____

By: _____ _____
Matthias Schmid Huberty, administrative director Swiss TPH *(Signature)*