Efficacy and Safety of Ivermectin and Albendazole Co-administration in School-aged Children and Adults Infected with *Trichuris Trichiura*: a Multi-country Randomized Controlled Trial

Trial registration number: NCT 03527732

Study protocols and SAP

Document date 24 November 2021

I. Table of content

1. Supplement overview

This supplement contains the following items:

1) An overview on protocol versions and history of protocol changes
2) Original protocol approved by the ethical committee of northwestern Switzerland (EKNZ) 05.05.2018. This protocol is the most comprehensive version and includes procedures for all three study countries.
3) Final protocol Pemba
4) Final protocol Côte d'Ivoire
5) Final protocol Laos
6) Statistical analysis plan (original statistical plan= final statistical analysis plan)

In every study country (i.e. Côte d'Ivoire, Laos and Pemba Island/Tanzania) country-specific protocols were submitted in different language versions (French in Côte d'Ivoire, Lao in Laos and English in Pemba Island). The final country versions differ from this version with respect to the following points:

Variations of country-specific protocols compared to this protocol:

- Côte d'Ivoire: The dose-finding sub study was removed from the protocol including all related objectives and procedures. The collection of stool sub samples for microbiome analysis was added to the protocol. Diagnosis of *Strongyloides stercoralis* was never considered for this country.

- Laos: The dose-finding sub study was never part of the protocol including all related objectives and procedures. Rapid testing for *Wuchereria bancrofti* was never considered for this country. The collection of stool sub samples for microbiome analysis and reporting of medical findings (blood parameter evaluation) back to participants was added to the protocol. We emphasized in the protocol that refusal to provide venous blood was not an exclusion criterion. Age in girls for pregnancy testing was raised from 10 to 12 years and older.

- Pemba Island: The dose-finding sub study was never part of the protocol including all related objectives and procedures. Venous blood sampling, rapid testing for *Plasmodium* spp. and diagnosis of *S. stercoralis* infections were never considered for this country. The collection of stool sub samples for microbiome analysis was added to the protocol.

2. Protocol versions and history of protocol changes

Country	Protocol version date	Date of (re-) submission/Name of IEC	Date accepted by IEC	Date of submission/Name of author authority	Date accepted author authority
Pemba/Tanzania	13.02.2018	21.02.2018/ZAMREC	23.05.2018		
Laos (1st submission)	18.06.2018	27.07.2018/NECHR			
Laos (re-submission after comments)	19.09.2018	19.09.2018/NECHR	23.10.2018		
Côte d'Ivoire (1st submission)	12.04.2018	20.04.2018/CNESVS	03.07.2018 accepted / 10.09.2018 suspended	13.07.2018/DPML	09.08.2018 trial suspended
Côte d'Ivoire (re-submission after comments and suspension by DPML)	22.11.2018	07.01.2019/CNESVS	24.01.2019	06.02.2019/DPML	22.03.2019
Switzerland	12.06.2018	13.06.2018/EKNZ	05.07.2018		

Abbreviations: IEC, Independent Ethics Committee; EKNZ, Ethikkomission Nordwest- und Zentralschweiz ; CNESVS, Comité National d'Ethique des Sciences de la Vie et de la Santé; DPML, Direction de la Pharmacie, du Médicament et des Laboratoires ; NECHR, National Ethics Committee for Health Research; ZAMREC, Zanzibar Medical Research and Ethics committee

Change	Timepoint of change	Country/Protocol version including change	Change in procedures
Additional secondary outcome: optimal timepoint for efficacy assessment (daily stool sampling)	12.06.2018	Switzerland (EKNZ accepted version/12.06.2018), Laos (resubmitted and accepted version/19.09.2018), Côte d'Ivoire (resubmitted and DPML accepted version/22.11.2018)	A subsample of 30 participants in each treatment arm (total 60 participants) will be asked to provide a daily stool sample for a period of up to 4 weeks to monitor dynamics of T. trichiura egg output for subsequent determination of the optimal timing for drug efficacy assessment.
Precision secondary outcome: To characterize *T. trichiura* strains from different epidemiological settings and investigate potential resistance markers using a deep sequencing analysis	12.06.2018	Switzerland (EKNZ accepted version/12.06.2018), Laos (resubmitted and accepted version/19.09.2018), Côte d'Ivoire (resubmitted and DPML accepted version/22.11.2018)	No changes in sampling procedure, but samples may be shipped to additional labs specialized in deep sequencing and resistance marker analysis.
Further elaborated description of data management and data quality control plan	13.06.2018	Switzerland (EKNZ accepted version/12.06.2018), Laos (resubmitted and accepted version/19.09.2018), CI (resubmitted and DPML accepted version/22.11.2018)	updated material transfer agreement and SOPs
additional secondary outcome: microbiome assessment	19.09.2018	Laos (resubmitted and accepted version/19.09.2018), Côte d'Ivoire (resubmitted and DPML accepted version/22.11.2018)	An additional aliquot of 1.5-2 g from each stool specimen will be frozen, shipped to and analyzed in Switzerland.
Precision exclusion/inclusion criteria: below age 6 and 15 kg body weight	19.09.2018	Laos (resubmitted and accepted version/19.09.2018), Côte d'Ivoire (resubmitted and DPML accepted version/22.11.2018)	Additional check for weight below 15kg on treatment days
Split of Côte d'Ivoire study protocol into two separate protocols: i) multi-country trial comparable to Pemba and Laos, ii) dose-finding study for ascending doses of IVM (200, 400 and 600 µg/kg) with single ALB (400mg) vs. Placebo	22.11.2018	Côte d'Ivoire (resubmitted and DPML accepted version/22.11.2018)	The IVM-ALB vs. ALB efficacy trial in 6-60 year olds was separately resubmitted to ethical committee of Côte d'Ivoire and DPML and received respective approvals on the 24.01.2019 and 22.03.2019. The second submission including the dose-finding trial of ascending doses of ivermectin with albendazole (400mg) was suspended by DPML (decision from 22.03.2019) until today.

3. Original protocol approved by the Swiss Ethics committee (EKNZ)

Efficacy and safety of ivermectin and albendazole co-administration in school-aged children and adults infected with *Trichuris trichiura*: a multi-country randomized controlled trial

Protocol Number	1		
Version Number	1.01	**Document Date**	12.06.2018
Sponsor Contact	Prof. Dr. Jennifer Keiser, Swiss Tropical and Public Health Institute, Tel.: +41 61 284-8218 Fax: +41 61 284-8105 E-mail: jennifer.keiser@unibas.ch		
Principle Investigator	Prof. Dr. Jennifer Keiser, Swiss Tropical and Public Health Institute, Tel.: +41 61 284-8218 Fax: +41 61 284-8105 E-mail: jennifer.keiser@unibas.ch		
Funding Agency	Bill and Melinda Gates Foundation		

1. General information

I. List of investigators and other persons involved

Title	Names	Institution	Position	Function in trial
Prof. Dr.	Jennifer Keiser	Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland	Unit head	Principal Investigator
Dr.	Eveline Hürlimann	Swiss TPH	Postdoc	Co-PI
Dr.	Jessica Schulz	Swiss TPH	Postdoc	Co-PI
Dr.	Jean Coulibaly	Swiss TPH / Université Félix Hophouët-Boigny (UFHB), Abidjan, Côte d'Ivoire	Group leader	Co-PI
Dr.	Yves N'Gbesso	Departement d'Agboville, Centre de Santé Urbain d'Azaguié, Azaguié	Medical doctor	Study physician
Dr.	Jan Hattendorf	Swiss TPH	Project leader	Statistician

II. Signatures

Statistician

Signature		Date of Signature 12.06.2018
Name	Jan Hattendorf	
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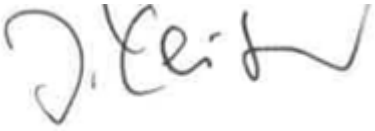
Institution	Swiss Tropical and Public Health Institute	
Address	Department of Medical Parasitology and Infection Biology Swiss Tropical and Public Health Institute, Socinstr. 57	
Phone	+41 61 284-8193	

Principal investigator

Signature		Date of Signature 12.06.2018
Name	Jennifer Keiser	
Title	Prof.	
Institution	Swiss Tropical and Public Health Institute	
Address	Department of Medical Parasitology and Infection Biology Swiss Tropical and Public Health Institute, Socinstr. 57	
Phone	+41 61 284-8218	

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-Principal investigator

Signature		Date of Signature 12.06.2018
Name	Eveline Hürlimann	
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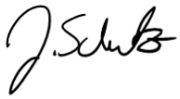
Co-Principal investigator

Signature		Date of Signature 12.06.2018
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III. Abbreviations

AE	Adverse event
AUC	Area under the curve
CI	Confidence interval
CNER	Comité Nationale d'Ethique de la Recherche
CR	Cure rate
CRF	Case report form
CSRS	Centre Suisse de Recherches Scientifiques en Côte d'Ivoire
DF	Dose-finding
DPML	Direction de la Pharmacie, du Médicament et des Laboratoires
EKNZ	Ethikkomission Nordwest- und Zentralschweiz
EML	Essential medicine list
EPG	Eggs per gram
ERR	Egg reduction rate
GCP	Good clinical practice
GEE	Generalized estimating equation
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
MDA	Mass drug administration
MIC	Minimal inhibitory concentration
MUAC	Mid-upper arm circumference
PC	Preventive chemotherapy
PCR	Polymerase chain reaction
PI	Principal investigator
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/pharmacodynamic
RDT	Rapid diagnostic test
SAE	Serious adverse event
SOP	Standard operating procedure
STH	Soil-transmitted helminth
Swiss TPH	Swiss Tropical and Public Health Institute
SUSAR	Suspected unexpected serious adverse reaction
WHO	World Health Organization

IV. Synopsis

Sponsor/Sponsor-Investigator	Prof. Dr. Jennifer Keiser
Study Title	Efficacy and safety of ivermectin and albendazole co-administration in school-aged children and adults infected with *Trichuris trichiura*: a multi-country randomized controlled trial
Short title	Efficacy and safety of IVM/ALB co-administration
Protocol Number, Date and Version	1, 12.06.2018, v1.01
Trial registration	Has been registered on ClinicalTrials.gov (reference: NCT 03527732)
Clinical phase	Phase 3 trial
Sample size	1960 (600 participants in each of 3 settings for the parallel group trial including 160 participants for the dose-finding (DF) study)
Indication	*Trichuris trichiura* infection (eggs in stool)
Investigational Product and Reference Treatment	Ivermectin and albendazole
Study Rationale	To provide evidence on a) potentially enhanced efficacy by combining the standard drug albendazole with ivermectin in school-aged children and adults against infection with *T. trichiura*. b) effective doses of ivermectin in combination with albendazole in school-aged children against infection with *T. trichiura*.
Study Objectives	To compare the efficacy and safety of: (a) standard doses of co-administered ivermectin (200 µg/kg) and albendazole (400 mg) compared to albendazole (400 mg) monotherapy in community members aged 6-60 years and (b) ascending doses of ivermectin ((i) 200 µg/kg, (ii) 400 µg/kg, and (iii) 600 µg/kg) co-administered with albendazole (400 mg) in school-aged children (6-12 years) infected with *T. trichiura* and to measure ivermectin and albendazole disposition in children using a microsampling device.

	Our **primary objective** is to comparatively assess the efficacy in terms of cure rates (CRs) against *T. trichiura* infections among school-aged children and adults of the following oral treatment regimens: a) in a parallel group trial: Albendazole (400 mg)/ivermectin (200 µg/kg) combination Albendazole (400 mg) monotherapy b) in the DF study (school-aged children only): Albendazole (400 mg)/ivermectin (200 µg/kg) combination Albendazole (400 mg)/ivermectin (400 µg/kg) combination Albendazole (400 mg)/ivermectin (600 µg/kg) combination Placebo The **secondary objectives** of the trial are: a) To evaluate the safety and tolerability of the treatment regimens b) To compare the egg reduction rate (ERR) of the treatment regimens (combination *vs*. monotherapy and ascending doses of the combination) against *T. trichiura* c) To determine the CRs and ERRs of the drugs in study participants (6-60 years) infected with hookworm, *Ascaris lumbricoides* and *Strongyloides stercoralis* d) To investigate potential extended effects on follow-up helminth prevalences (6 and 12 months post-treatment) of the two standard-dose treatment regimens (as assessed among participants with cleared infection on days 21 and 180) e) To compare CRs based on infection status determined by novel polymerase chain reaction (PCR)-based and standard microscopic diagnosis f) To assess potential differences in susceptibility to the treatment regimen between the hookworm species, *Necator americanus*, *Ancylostoma duodenale* and *A. ceylanicum*, as classified through the novel PCR-based diagnosis g) To characterize *T. trichiura* strains from different epidemiological settings and investigate potential resistance markers using a deep sequencing analysis

	h) To determine optimal timing for measuring anthelmintic efficacy in *T. trichiura* infection i) To evaluate potential benefits from deworming on morbidity indicators and nutritional parameters j) To determine an exposure (including length of time that the drug concentration is above the minimal inhibitory concentration (MIC), Cmax, area under the curve (AUC))-response correlation of ivermectin and albendazole in school-aged children
Study design	Double blind, randomized controlled trial
Study product / intervention	Administration of a single oral dose of ivermectin + albendazole
Comparator(s)	main trial: albendazole (400 mg) monotherapy, DF study: placebo
Key inclusion / Exclusion criteria	**Inclusion:** School-aged children and adults (6-60 years) infected with *T. trichiura* with at least two slides of the quadruple Kato-Katz thick smears positive and infection intensities of at least 100 eggs per gram of stool (EPG), agreeing to comply with study procedures, including provision of two stool samples at the beginning (baseline) and on three follow-up assessments (approximately 3 weeks, 6 months, and 12 months later), written informed consent signed by parents and/or caregivers for children/adolescents; and written assent by child/adolescent (aged 6-20 years). **Exclusion:** No written informed consent by individual/parents and/or caregiver, any clinically relevant abnormality (including severe anemia or clinical malaria) or history of acute or severe chronic disease (*e.g.* cancer, diabetes, chronic heart, liver or renal disease), recent use of anthelminthic drug (past 4 weeks), attending other clinical trials during study, negative diagnostic or low egg count (less than 100 EPG or less than 2 out of 4 slides positive) result for *T. trichiura*, known allergy to study medication, pregnancy or lactating in the 1st week after birth, taking medication with known interaction on study drugs.
Primary Endpoints	*T. trichiura* infection status assessed by Kato-Katz 14-21 days after treatment
Secondary Endpoints	• ERR against *T. trichiura* • CRs and ERRs against *A. lumbricoides*, hookworm and *S. stercoralis* • Adverse events • Infection status assessed by PCR • Pharmacokinetic parameters for ivermectin and albendazole in school-aged children

Exploratory Endpoints	• Molecular characterization and resistance markers of *T. trichiura* • Optimal timing for drug efficacy assessment in *T. trichiura* infection • Nutritional status • Morbidity indicators
Interim Analyses	None
Study Duration	14 months
Schedule	06/2018 of first-participant in (planned) 08/2019 of last-participant out (planned)
Study centers	Multinational study with trial sites in Côte d'Ivoire, Lao PDR and Pemba Island (Tanzania)
Measurements & procedures	Two stool samples (each of a minimum of 15 grams) will be collected if possible on two consecutive days or otherwise within a maximum of 5 days. The medical history of the participants will be assessed with a standardized questionnaire, in addition to a clinical examination carried out by the study physician before treatment. All participants will be interviewed before treatment, 3 and 24 hours and 3 weeks after treatment about the occurrence of adverse events. Children aged 6-16 years will additionally be asked to rate their own physical functioning by replying to a pre-tested questionnaire at baseline and 6 and 12 months after treatment. The efficacy of the treatment and potential extended effects on follow-up prevalence will be determined 14-21 days, 6 months and 12 months post-treatment by collecting another two stool samples. Subjective treatment satisfaction will be assessed 3 hours, 3 weeks and 6 months after treatment to investigate relationship with treatment compliance and observed efficacy in reducing egg output and morbidity. All stool samples will be examined with duplicated Kato-Katz thick smears for *T. trichiura*, *A. lumbricoides* and hookworm. *S. stercoralis* infections will be identified using the Baermann technique and recorded qualitatively as larvae-positive or negative. For subsequent PCR-analysis a portion of 1.5-2 g of stool from each specimen will be preserved in 70% ethanol and shipped to a reference laboratory at Swiss TPH in Switzerland. At baseline and in the first follow-up (3 weeks post treatment) an additional portion of stool (1.5-2 g) from a subsample of 10 participants identified with heavy intensity infections in each case and study setting will be preserved in 95% ethanol, shipped to the same reference laboratory and subjected to deep sequencing for characterization of *T. trichiura* strains and investigation of potential resistance markers. Fecal occult blood and calprotectin in stool as markers for gut morbidity and inflammation will be detected using a rapid diagnostic test and an immunoassay, respectively. A subsample of 30 participants will be asked to provide a daily stool sample for a period of up to 4 weeks to monitor dynamics

	of *T. trichiura* egg output for subsequent determination of the optimal timing for drug efficacy assessment. Individuals found *T. trichiura* positive 6 months after baseline will receive a second round of treatment according to their group scheme. Each participant will be asked to provide a finger-prick blood sample for hemoglobin measurement, a rapid diagnostic test (RDT) for *Plasmodium* spp. and where applicable a biplex RDT for lymphatic filariasis/onchocerciasis at baseline and 6 and 12 months after treatment. At the same time points anthropometric measurements (*i.e.* height, weight, mid-upper arm circumference (MUAC) and skinfold thickness) will be taken for all participants. In addition, a venous blood sample (~8 ml) will be taken from each participant to assess biochemical blood parameters as proxies for vital organ functioning (*e.g.* complete blood count, urea, creatinine, transaminases etc.) and nutritional indicators for micro- (*i.e.* (pro-) vitamins, inflammation markers, and iron/ferritin) and macronutrient (*i.e.* albumin) deficiencies at baseline, day 21, day 180 and day 360. To all participating households, a questionnaire will be administered assessing information on socioeconomic characteristics and access to sanitation, water facilities, and hygiene behavior. For the assessment of pharmacokinetic parameters within the DF study the participating school-aged children (6-12 years) will be sampled using finger pricking for microsampling at 0, 1, 2, 3, 4, 5, 6, 7, 9, 24, 48 hours post-dosing.
Statistical Analyses	An available case analysis 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 egg-positive subjects at baseline who become egg-negative after treatment. Differences among CRs (between treatment arms and between diagnostic approaches) will be analysed by using crude and adjusted logistic regression modeling (adjustment for age, sex and weight). Geometric and arithmetic mean egg counts will be calculated for the different treatment arms before and after treatment to assess the corresponding ERRs. Bootstrap resampling method with 5,000 replicates will be used to calculate 95% confidence intervals (CIs) for differences in ERRs. Further secondary outcomes – as nutritional and morbidity indicators - will be analysed using logistic and linear regression as appropriate. To compare individual's changes in nutrition/morbidity categories as an effect from treatment McNemar's test will be applied. The analysis after 6 and 12 month of follow-up will be complemented by generalized estimating equation (GEE) models with independent correlation structure and empirical estimators to account for missing data. Nonlinear mixed-effects modeling will be used to determine pharmacokinetic parameters.

GCP statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ICH-GCP E6 (R2) as well as all national legal and regulatory requirements.
Key explanation for the inclusion of children	This study will involve school-aged children, since an infection with *T. trichiura* occurs most often in children and they are further the main target group of deworming campaigns.
Recruitment procedure	The parallel group trial will be conducted as a multi-country study with two settings in Africa and one in Asia recruiting each 600 community members: • West African setting: Côte d'Ivoire • East African setting: Pemba (Zanzibar, Tanzania) • Asian setting: Lao PDR The DF study will be embedded in the trial and implies the recruitment of an additional 160 school-aged children (6-12 years) to be able to include 40 children per arm in Côte d'Ivoire. The studies will be conducted in areas with moderate to high *T. trichiura* endemicity (communities with a prevalence ≥ 25%) identified from earlier studies and/or based of experience of the local collaborating teams. They will be implemented as community-based studies in order to recruit participants from a broad age range (6-60 years). Ideally, entire communities with a population size of < 1000 inhabitants will be included in the study for pre-screening and identification of *T. trichiura* cases to avoid potential selection bias of households. To identify all potentially eligible households of the respective communities and its composition in terms of age groups a preceding population census will be conducted.
Coverage of damages	Winterthur Police Nr. 4746321, BERACA Côte d'Ivoire, No: to be issued
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.

2. Background information

Albendazole and mebendazole are the most widely used drugs for preventive chemotherapy (PC) campaigns against soil-transmitted helminth (STH) infections. Albendazole is characterized by high cure rates (CRs) and egg reduction rates (ERRs) against infections with *Ascaris lumbricoides* (95.7% and 98.5%) and hookworm infections (79.5 and 89.6%). Lower efficacy is observed against *Trichuris trichiura* infections (CR 30.7%, and ERR of 49.9%) [1].

Therapies combining two or more drugs are widely advocated in different therapeutic areas such as tuberculosis, malaria, HIV/AIDS or cancer. The underlying rationale for multifactorial pharmacological treatment varies with the disease and includes the protection against the selection of drug-resistance, and hence, a prolongation of the life-span of effective and available drugs, and to increase and broaden the efficacy over drugs being administered in mono-therapy [2].

A recent review and meta-analysis found that ivermectin co-administered with albendazole is highly efficacious for the treatment of *T. trichiura* and is comparatively more efficacious than albendazole alone (Figure 1) [3]. Efficacy of ivermectin and albendazole against *A. lumbricoides* and hookworm are comparable and in some cases more efficacious than albendazole alone. Summarized efficacy measures of albendazole, mebendazole, and ivermectin against trichuriasis from a recent review [1] and earlier trials [4, 5] are shown in Table 1.

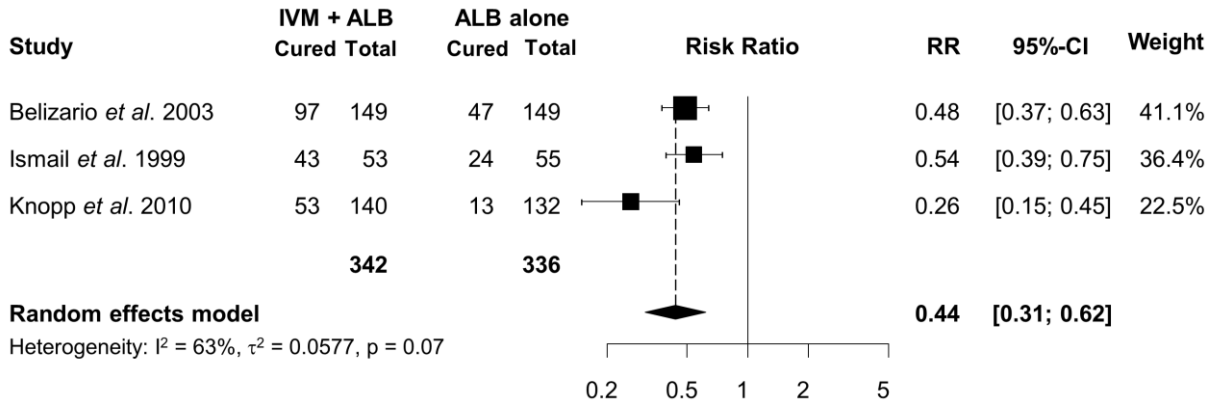

Figure 1. Forest plot displaying the results of a random-effects meta-analysis of the effect of the co-administration of albendazole-ivermectin on the number of patients infected with *T. trichiura* compared to albendazole alone.

Table 1. Average CRs and ERRs of albendazole and mebendazole for *T. trichiura* from a recent review [1] as well as findings from studies investigating ivermectin [4, 5]

Drug	CR (%)	95% CI	ERR (%)	95% CI
Albendazole	30.7	(21.0, 42.5)	49.9	(39.0, 60.6)
Mebendazole	42.1	(25.9, 60.2)	66.0	(54.6, 77.3)
Ivermectin	11-35	NA	43-98	NA

NA, not applicable

The individual studies included in the review are summarized in Table 2. All four studies are randomized controlled trials and used the standard dose of 200 µg/kg ivermectin and 400 mg albendazole [4, 6-8]. Against infections with *T. trichiura*, CRs ranging from 27.5-81.1%, ERR based on geometric mean ranging from 91.3-99.7%, and ERR based on arithmetic mean ranging from 85.6-97.5% were observed. CRs for *T. trichiura*

observed in Asian settings were higher than in African settings. One reason for this finding may be differences in the study design and quality (*e.g.* in terms of diagnostic approach used). Another possible reason recently highlighted is genetic diversity of *T. trichiura* strains and variation in susceptibility to anthelmintics and/or drug resistance [9-11]. Interestingly, the higher efficacy of ivermectin in combination with albendazole translated – at least in some settings – into lower prevalences even after one year [4, 12]. The efficacy of albendazole-ivermectin against *A. lumbricoides* was excellent (CRs >78% and ERRs >99.5%), while moderate CRs (50-66.7%) and high ERRs (>95.4%) were observed against hookworm.

Table 2. Known efficacy of co-administered ALB-IVM[a] against *T. trichiura*:

Study	**Setting**	**Cure rate in % (n_{neg}/n)**	**Eggs per gram (pre/post)**	**Egg reduction rate in %**
Ismail et al. 1999	Sri Lanka	81.1% (43/53)	1544.0/78.7 (unkwn)	94.9% (unkwn)
Belizario et al. 2003	Philippines	65.1% (97/149)	4948.1/122.5 (ar) 550.0/1.9 (geo)	97.5% (ar) 99.7% (geo)
Knopp et al. 2010	Tanzania (Pemba)	37.9% (53/140)	127/11 (geo)	91.3% (geo)
Speich et al. 2015	Tanzania (Pemba)	27.5% (30/109)	1059/153 (ar) 489/27 (geo)	85.6% (ar) 94.5% (geo)
All studies		**49.4% (223/451)**		

[a]*Considered doses: albendazole=400 mg, ivermectin=200 µg/kg*

ar=arithmetic mean, geo=geometric mean, unkwn=unknown mean

The WHO Expert Committee met from March 27-31, 2017 and, based on review of a dossier suggesting inclusion of ivermectin as an anthelmintic in the Essential Medicines List, made the following recommendation:

"…adding ivermectin on the Essential Medicines List under the section intestinal anthelminthic for use against Strongyloides stercoralis and STH. It may be used in combination with albendazole for treatment of soil-transmitted helminthiasis."

This important milestone paves the way for further, standardized trials to evaluate the efficacy of this combination among school-aged children in a range of epidemiological settings. In addition, the combination should be evaluated among adults, as there is growing interest in broadening deworming to include adults in order to move from morbidity control toward interruption of transmission [13, 14].

In the proposed work, three trials are planned across a range of transmission settings, including Côte d'Ivoire, Lao PDR, and Pemba (Tanzania). Follow-up will be conducted at 1, 6, and 12 months to inform treatment frequency. Results from these trials will inform decisions on how the combination could be introduced into existing mass drug administration (MDA) programs and therefore provide a valuable adjunct tool for interrupting STH transmission.

3. Trial objective and purpose

The overall goal of the study is to assess the efficacy and safety of co-administered albendazole and ivermectin versus albendazole monotherapy (standard of care) against *T. trichiura* infections in children and adults (6-60 years) in different transmission settings and geographies. Embedded in this trial a smaller dose-finding (DF) study with the goal to investigate efficacy, safety and pharmacokinetic parameters of ascending doses of ivermectin ((i) 200 µg/kg, (ii) 400 µg/kg, and (iii) 600 µg/kg) co-administered with albendazole (400 mg) in school-aged children infected with *T. trichiura* will take place.

We hypothesize that albendazole-ivermectin has a higher efficacy against *T. trichiura* infections than albendazole alone, and hence, the efficacy against all three STH species (*A. lumbricoides*, *T. trichiura*, and hookworm) and *Strongyloides stercoralis* will be increased.

The **primary objective** of the trial is to comparatively assess the efficacy in terms of CR against *T. trichiura* infections among school-aged children and adults from three different epidemiological settings and monitored over a 12-month period of the following two oral treatment regimens:

- Albendazole/ivermectin combination
- Albendazole monotherapy

A DF study will be implemented in the trial with the objective to understand the dose-dependent efficacy and pharmacokinetic profile of the co-administration of albendazole and ivermectin in school-aged children (6–12 years) with the following four oral treatment regimens:

- Albendazole (400 mg) /ivermectin (200 µg/kg) combination
- Albendazole (400 mg) /ivermectin (400 µg/kg) combination
- Albendazole (400 mg) /ivermectin (600 µg/kg) combination
- Placebo

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

a) To evaluate the safety and tolerability of the treatment regimens
b) To compare the ERRs of the treatment regimens (combination *vs*. monotherapy and ascending doses of the combination) against *T. trichiura*
c) To determine the CRs and ERRs of the drugs in study participants (6-60 years) infected with hookworm, *A. lumbricoides* and *S. stercoralis*
d) To investigate potential extended effects on follow-up helminth prevalences (6 and 12 months post-treatment) of the two standard-dose treatment regimens (as assessed among participants with cleared infection on days 21 and 180)
e) To compare CRs based on infection status determined by novel polymerase chain reaction (PCR)-based and standard microscopic diagnosis
f) To assess potential differences in susceptibility to the treatment regimen between the three hookworm species, *Necator americanus, Ancylostoma duodenale and A. ceylanicum*, as classified through the novel PCR-based diagnosis
g) To characterize *T. trichiura* strains from different epidemiological settings and investigate potential resistance markers using a deep sequencing analysis
h) To determine optimal timing for measuring anthelmintic efficacy in *T. trichiura* infection
i) To evaluate potential benefits from deworming on morbidity (clinically evaluated and self-rated from questionnaire interviews) and nutritional indicators

j) To determine an exposure (including length of time that the drug concentration is above the minimal inhibitory concentration (MIC), Cmax, area under the curve (AUC))-response correlation of ivermectin and albendazole in school-aged children

4. Methodology

4.1 Primary and secondary endpoint

T. trichiura infection status assessed by Kato-Katz 14-21 days after treatment will be the primary endpoint and the main outcome for efficacy be expressed as cure rate (CR) (*i.e.* conversion from being egg positive pre-treatment to egg negative post-treatment) and egg reduction rate (ERR) (secondary end point). Secondary endpoints include further infection status with *A. lumbricoides*, hookworm and *S. stercoralis* and related efficacy measures, adverse events, infection status assessed by PCR and key pharmacokinetic parameters in school-aged children. In addition, optimal timing for drug efficacy assessment in *T. trichiura* infection will be determined, *T. trichiura* strains will be described and potential resistance markers evaluated using deep sequencing and potential benefits on nutritional and morbidity indicators from treatment assessed (exploratory end points).

4.2 Type of trial

Double blind randomized controlled trial.

4.3 Trial design

4.3.1 Baseline survey and screening

Parallel group multi-country study

A randomized-controlled trial will be conducted with two treatment arms to be followed-up over a 12 months period with an intermediate re-treatment of participants found re-infected after 6 months (Figure). This parallel group trial will be conducted as a multi-country study; thus, in each setting a separate trial according to the design described below will be set up, to provide a better basis for the subsequent generalization of its findings. This arises from the possibility of recruiting the subjects from a wider population and of administering the medication in a broader range of clinical settings, thus presenting an experimental situation that is more typical of future use. The study includes one baseline and three follow-up assessments at 3 weeks (day 21), 6 months (day 180), and 12 months (day 360).

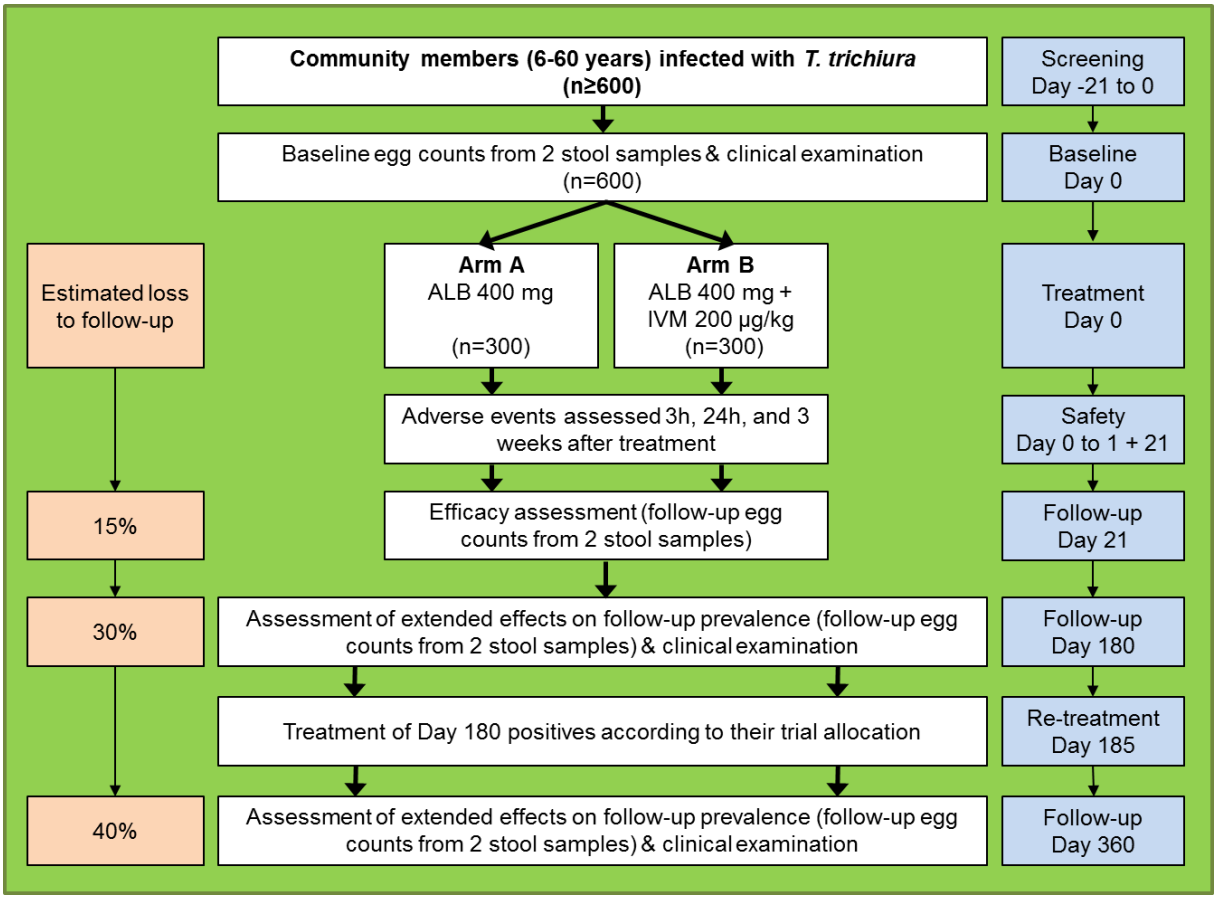

Figure 2. Design and timeline of the randomized-controlled trial to be implemented in each of three settings.

The study is designed as a two-armed trial including one arm with a single drug administration (arm A; albendazole) and one arm with combined treatment through co-administration of separate tablets (arm B; albendazole and ivermectin).

The trial will be conducted as a multi-country study with two settings in Africa and one in Asia, namely Côte d'Ivoire, Pemba (Zanzibar, Tanzania) and Lao PDR.

At baseline, all participants will be asked to provide two stool samples of at least 15 grams each (within a maximum of 5 days). From every stool specimen, duplicate Kato-Katz thick smears (41.7 mg each) [15] will be prepared and read under a microscope for eggs of *T. trichiura*, *A. lumbricoides* and hookworm by experienced technicians. A small amount of feces (~10 mg and 60 µg, respectively) will further be tested on fecal occult blood and calprotectin as proxies for gut morbidity and inflammation using a rapid diagnostic test an immunoassay, respectively [16]. Additionally, a portion of 1.5-2 g of stool from each specimen will be preserved in 70% ethanol and shipped to a reference laboratory at the Swiss Tropical and Public Health Institute (Swiss TPH, Basel, Switzerland) for PCR analysis [17]. While discrimination of hookworm species via morphological comparison during microscopy of Kato-Katz slides is not feasible [18], PCR will allow to accurately determining efficacy and for further classification of hookworm infection into the three species *N. americanus, A. duodenale* and *A. ceylanicum*. The remains of each stool sample (ideally 10 to 20 g) will be processed by the Baermann technique for identification of *S. stercoralis* infections and be recorded qualitatively as larvae-positive or negative. At baseline and in the first follow-up (3 weeks post treatment) an additional portion of the second stool sample (1.5-2 g) from a subsample of 10 participants identified with heavy intensity infections in each case (as assed on the first sample) will be preserved in 95% ethanol, shipped to the same reference laboratory at Swiss TPH in Switzerland and subjected to deep sequencing for characterization of *T. trichiura* strains and

investigation of potential resistance markers [19]. A subsample of 30 participants will be asked to provide a daily stool sample for a period of up to 4 weeks to monitor dynamics of *T. trichiura* egg output for subsequent determination of the optimal timing for drug efficacy assessment as has been done for other STH species earlier [20].

A subsequent independent quality control of sample results (approximately 10%) will be conducted. Results are considered correct if the following tolerance margin is not exceeded: (i) No difference in presence/absence of hookworm, *A. lumbricoides* and *T. trichiura*, (ii) egg counts are +/-10 eggs for counts ≤100 eggs or +/-20% for counts >100 eggs (for each species separately) [21]. 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 count per gram of stool (EPG) will be calculated for each treatment arm. All microscopically analyzed quadruplicate Kato-Katz thick smears will be destroyed within one day (after passing the quality control). The same sampling procedure and diagnostic approach will be applied at days 21, 180 and 360 post-treatment.

Patients with filariasis showed significantly higher numbers of adverse events (AE) for treatment with ivermectin in combination with albendazole in earlier studies [22-24]. A rapid diagnostic test (RDT; *i.e.* SD BIOLINE Oncho/LF IgG_4 biplex test) to detect antigens in the blood will therefore be used to identify potential co-infection with *Wuchereria bancrofti* and *Onchocerca volvulus* at baseline, 6 and 12 months post-treatment (before a potential re-treatment). AEs after treating filariasis were mostly mild [3]; the approach of capturing AEs will thus not change but the result of the RDT be used to explain potential differences in AE reporting between filariasis negative and positive participants.

A clinical examination of the study participants assessing general health, anthropometric parameters including height, weight, mid-upper arm circumference (MUAC) and skinfold thickness (i.e. triceps and subscapular skinfolds) as well as tympanic temperature using an ear thermometer will precede the treatment and will be repeated on two follow-up assessments (days 180 and 360) to evaluate potential benefits from deworming. Each participant will be asked to provide a finger-prick blood sample for a RDT for *Plasmodium* spp. infection and to evaluate hemoglobin (Hb) levels using a HemoCue analyzer (Hemocue Hb 301 system; Angelholm, Sweden) following the same (re-)assessment schedule. To assess potential improvement on nutritional indicators for micro- (*i.e.* (pro-) vitamins, inflammation markers, and iron/ferritin) and macronutrient (*i.e.* albumin) deficiencies and dynamics of biochemical blood parameters as a proxy for functioning of vital organs a venous blood sample (approximately 8 ml) will be taken at baseline, day 21, day 180 and 360. The biochemical parameters to be assessed include urea, creatinine, bilirubin, azotemia, Alanine Amino Transferase (ALAT), Aspartate Amino Transferase (ASAT) as well as blood cell counts (*e.g.* hematocrit, erythrocytes and platelets). To avoid accidental treatment of pregnant girls/women all female participants (≥ 10 years) will be asked to provide a urine sample of at least 10 ml to be subjected to a pregnancy RDT on day 0 and day 180.

All trial participants will further be asked about existing clinical symptoms before drug administration. Additionally, they will be asked to provide subjective short-term (*e.g.* convenience of treatment) and long-term (*e.g.* effectiveness in reducing symptoms) treatment satisfaction embedded in the re-assessment questionnaires. As a measure of patient-rated physical functioning and wellbeing all children (6-16 years) will be administered a questionnaire before, 6 and 12 months after treatment, based and adapted from tools already validated in school-aged children from rural settings in Côte d'Ivoire [25] and pre-tested in a comparable school-aged population not otherwise involved in this trial. To adjust for known influencing factors with regard to reinfection and morbidity [26, 27] in the subsequent analysis and to identify risk factors for residual infections [28] a household-based questionnaire will be administered to one adult member of each participating household, assessing information on socioeconomic characteristics, access to sanitation and water facilities as well as hygiene behavior.

DF study with school-aged children

Embedded in the parallel group trial a randomized-controlled DF study assessing ascending doses of ivermectin co-administered with a single dose of albendazole will be implemented. The study is designed as a four-armed trial including ascending doses of ivermectin co-administered with the standard dose of albendazole (arm 1–3) and one placebo arm serving as a comparator (arm 4) (Figure). 160 school-aged children infected with *T. trichiura* will be randomly assigned to arm 1–4. Baseline and screening procedures are identical to the parallel group study. Children in arm 1-3 will be micro sampled on different time points between treatment day 0 and day 2 (at 0, 1, 2, 3, 4, 5, 6, 7, 9, 24, 48 hours post-dosing) in order to obtain pharmacokinetic data while children in arm 4 will provide finger-prick blood samples at day 0 only for RDT assessments.

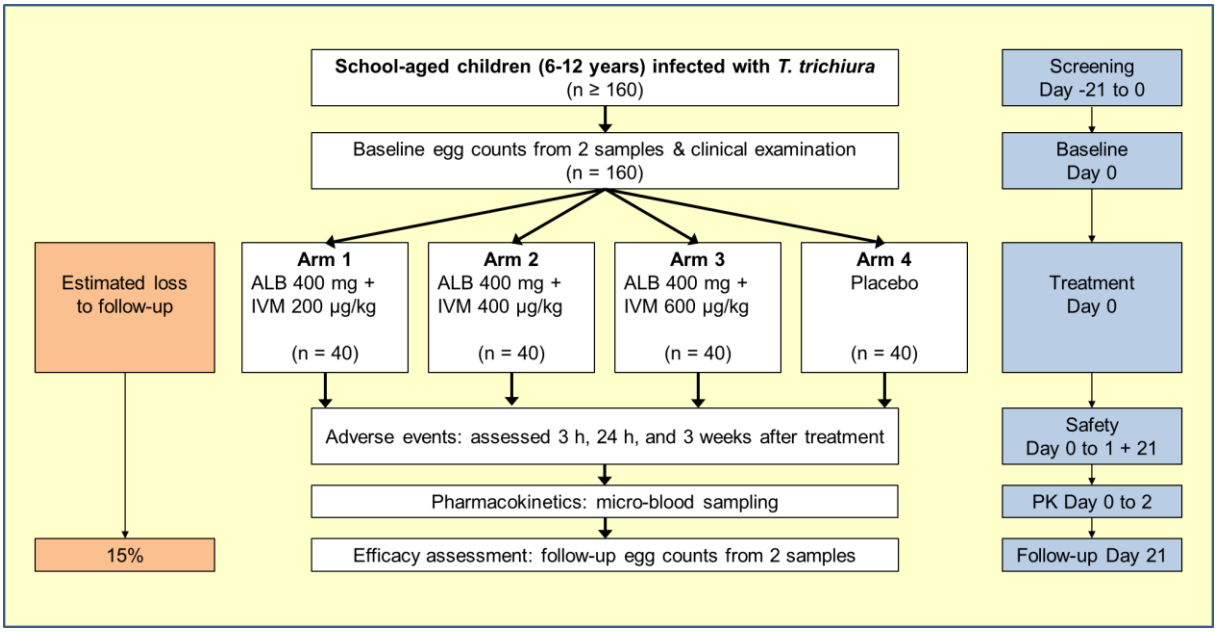

Figure 3. Efficacy, safety and pharmacokinetics of ivermectin-albendazole co-administration: dose-finding study flow.

4.3.2 Assessment of efficacy and other benefits after treatment

Parallel group multi-country and DF study

The efficacy of the treatment will be determined 21 days post-treatment by collecting another two stool samples which will be microscopically examined for *T. trichiura* using duplicate Kato-Katz thick smears and potential co-infection with *S. stercoralis* applying the Baermann technique. Participants will be considered *T. trichiura* cured if no eggs have been found in the stool. EPG will be assessed by adding up the egg counts from the quadruplicate Kato-Katz thick smears and multiplying this number by a factor of six. Geometric and arithmetic mean egg counts will be calculated for the different treatment arms before and after treatment to assess the corresponding ERRs. The stool samples collected 21 days post-treatment for efficacy assessment will further be re-tested with the same rapid diagnostic test and immunoassay used at baseline to determine fecal occult blood and calprotectin levels. Frequencies of subjects found positive with either of the two markers and by intensity category for calprotectin will be calculated by treatment arm.

At the end of the study (*i.e.* for exclusive DF study participants 1 month post-treatment, for trial participants 12 months post-treatment) all participants remaining positive for *T. trichiura*, other soil-transmitted helminths or filariasis will be treated with albendazole-ivermectin, the currently best approved and recommended treatment against *T. trichiura* [29].

Parallel group multi-country study

Potential extended effects on follow-up helminth prevalences will be assessed using the same methodological approach as used for the efficacy assessment and will be based on stool samples collected 6 and 12 months post-treatment. Likewise fecal occult blood and calprotectin will be re-determined on the same stool samples.

To assess eventual reduction in morbidity and improvement in nutritional indicators all trial participants will be asked to provide another finger-prick at the 6 and 12 month follow-up for Hb measurement and rapid diagnostic testing (*i.e.* malaria and filariasis) and once more a venous blood sample for micronutrient/blood parameter evaluation at all three follow-up time points, respectively. Anthropometric measurement including height, weight, MUAC and skinfold thickness will be repeated on the same occasion. Children (6-16 years) will be asked to re-assess their own physical functioning in repeated questionnaire interviews during these two last follow-ups. Long-term satisfaction with the treatment will be asked 6 months post-treatment. Mean values for continuous outcomes and frequencies for binary/categorical outcomes will be calculated for each treatment arm and follow-up time point and compared using descriptive and repeated measurement analysis as detailed in section 7.3.

4.3.3 Pharmacokinetic studies

DF study

The micro-sampling device dried blood spot (DBS) is a more robust, ethical and patient-friendly technique compared to venous blood sampling to evaluate the pharmacokinetic profile of a drug. In order to use DBS in a clinical trial, it first needs to be evaluated that the analysis of venous and capillary blood yields same drug concentrations. Therefore, plasma and DBS samples were previously collected in two independent clinical trials in rural Côte d'Ivoire with adult volunteers who received either the standard dose of albendazole (400 mg) or the standard dose of ivermectin (200 µg/kg). Methods to extract and quantify ivermectin in the different matrixes have been validated and applied to the samples of the adult volunteers. Results show consistent correlation of plasma and DBS samples so that DBS can be reliably used.

The micro-sampling device DBS will be used as a tool to evaluate the pharmacokinetic (PK) parameters of albendazole and ivermectin in the DF study of their co-administration in school-aged children. 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 0, 1, 2, 3, 4, 5, 6, 7, 9, 24, 48 hours post-dosing. A few drops of blood will be transferred at each time point on DBS filter paper (Whatman) and dried for approximately 1 hour. The DBS cards will be transported to Basel and stored at -80° C until analysis. Albendazole and its metabolites will be quantified using a 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 3 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.

4.4 Measure to minimize bias

For each study (*i.e.* parallel group trial and DF study) independently study participants eligible for treatment will be randomly assigned to one of the treatment arms using a computer-generated stratified block randomization code. The random allocation sequence with varying random blocks of four or eight and stratified by 2 levels of baseline infection intensity (light: <1000 EPG, and moderate plus heavy: ≥ 1000 EPG *T. trichiura* infections) will be provided by a statistician. The treatment arms will have an equal number of participants with light infection intensity, although the number of light versus moderate/heavy infections are not expected to be equal in each arm, depending on the distribution of infection intensity in the recruited cohort. The parallel group trial will be double blinded (*i.e.* study participants and the trial team/researchers conducting the treatment and assessing the outcomes will be blinded) using repacked tablets including appearance-matched placebos while the DF study will be single blinded (*i.e.* all outcome assessors except the investigators who provide the treatment and the study

participants who get either active or placebo tablets matching in appearance will be blinded) due to the nature of this study (*i.e.* including ascending doses).

4.5 Study duration and duration of subject participation

The trial will last fourteen months. The screening for the baseline will start three weeks prior to the treatment. Follow-up screening will take place 14-21 days, 180 days and 360 days post-treatment and last each time for about three weeks. Schedules of visits are summarized below.

4.6 Schedule of visits

Parallel group multi-country study

Table 3. Schedule of visits of parallel group study.

	Screening -21 to -1 days	**Baseline/Treatment/Safety** Hours 0		3	24	**Follow up** Days 21	180	185	360
Diagnosis (stool examination)	X					X	X		X
Gut morbidity (stool RDTs)	X					X	X		X
Informed consent	X								
Demographics	X								
Medical history		X							
Clinical examination		X					X		X
Pregnancy testing		X					X		
Hemoglobin measurement		X					X		X
***Plasmodium* co-infection**		X					X		X
***Filaria* co-infection**		X					X		X
Venous blood examination		X				X	X		X
Physical functioning		X					X		X
Capturing AEs				X	X	X			
Capturing SAE				X	X	X			
Treatment satisfaction				X		X	X		

Randomization and treatment (spans Hours 0 through 24)

Selective re-treatment (spans Days 185 through 360)

DF study

The general outline of the DF study is similar to the parallel group multi-country study with the following adaption: Follow-up will be performed 21 days after treatment only and micro-blood sampling will be performed 0–48 hours post treatment.

Table 4. Schedule of visits of dose-finding study.

	Screening					**Follow up**
	-21 to -1 days	Hours 0	Randomization and treatment	1-9	24	48	21 days
Diagnosis (stool examination)	X						X
Informed consent	X						
Demographics	X						
Medical history		X					
Clinical examination		X					
Rapid diagnostic tests		X					
PK sampling		X		X	X	X	
Capturing AEs				X (3h)	X		X
Capturing SAE				X (3h)	X		X

5. Selection of the trial subjects

5.1 Recruitment

The study will be carried out in community members aged 6–60 years in areas with moderate to high *T. trichiura* endemicity (communities with a prevalence ≥ 25%) identified from earlier studies and/or based on experience of the local collaborating teams. The trial will be implemented as community-based study in order to recruit participants from a broad age range (6–60 years). Ideally, entire communities with a population size of < 1000 inhabitants will be included in the study for pre-screening and identification of *T. trichiura* cases to avoid potential selection bias of households. To identify all potentially eligible households of the respective communities and its composition in terms of age groups a preceding population census will be conducted.

All adult community members, including parents/caregivers of minor participants, will be invited to participate in an information meeting to explain the purpose and procedures of the study, including potential benefits and risks. Parents/caregivers/potential participants will be encouraged to ask questions in an open discussion forum. During this session, they will be informed of preventive actions they can take to help protect their children from acquiring *T. trichiura* and other STH infections in the future (*e.g.* adequate food, preparation and defecation behavior).

Those parents/caregivers and their children 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. Written informed consent signed by either the participant him/herself (≥21 years of age) or by parents and/or caregivers for children/adolescents; and written assent by child/adolescent (aged 6–20 years).
2. Agree to comply with study procedures, including provision of two stool samples at the beginning (baseline) and on three follow-up assessments (approximately 3 weeks, 6 months, and 12 months later).
3. Aged ≥6 to ≤60 years for parallel group trial and ≥6 to ≤12 years for DF study.
4. At least two slides of the quadruple Kato-Katz thick smears positive for *T. trichiura* and infection intensities of at least 100 EPG.

5.3 Exclusion criteria

1. No written informed consent by individual/parents and/or caregiver.
2. Presence of major systemic illnesses, *e.g.* severe anemia (below 80 g/l Hb according to WHO [30]), clinical malaria as assessed by a medical doctor (positive *Plasmodium* RDT and ≥38 °C ear temperature), upon initial clinical assessment.
3. History of acute or severe chronic disease (*e.g.* cancer, diabetes, chronic heart, liver or renal disease).
4. Recent use of anthelmintic drug (within past 4 weeks).
5. Attending other clinical trials during the study.
6. Negative or low egg count (less than 100 EPG or less than 2 out of 4 slides positive) diagnostic result for *T. trichiura* eggs in the stool.
7. Known allergy to study medications (*i.e.* albendazole and ivermectin).
8. Pregnancy or lactating in the 1st week after birth (according to WHO guidelines within LF control programs [31]).
9. Currently taking medication with known interaction (*e.g.* for albendazole: cimetidine, praziquantel and dexamethasone; for ivermectin: warfarin).

5.4 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 a participant withdraws).

2. At the discretion of the Principal Investigator (PI) or co-PI, if the participant is not compliant to the requirements of the protocol.

Discontinued 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.

5.5 Treatment of subjects

Parallel group multi-country and DF study

All *T. trichiura*-infected, consenting, and participating community members will be treated with the respective single or combination treatment regimen at day 0. 400 mg albendazole will be the product of Glaxo Smith Kline

(Zentel®) and a single tablet administered. 3 mg tablets of ivermectin (Stromectol®) will be obtained from Merck, France, the weight recorded for each participant and the correct dose evaluated and administered. Matching ivermectin placebo tablets (in terms of appearance) will be produced and a certificate of manufacture and analysis be provided by the University of Basel. The tablets for the main trial, which is double-blinded, will be repacked into neutral separate plastic bags each containing one albendazole tablet and the maximum number of ivermectin tablets with regard to weight and dose or the corresponding number of placebo tablets. The ivermectin tablets for the dose-finding study will be kept in the original package until treatment day. Since albendazole and ivermectin are known to be better absorbed in humans after a high-fat meal was consumed, participants will receive a local high-fat breakfast (sandwich with *e.g.* oily sardines) prior to treatment [32, 33].

All drugs will be administered in the presence of the investigator(s), 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. The Principal Investigator 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.

Antimalarial treatment (*i.e.*, artemisinin-based combination therapy) will be provided to participants found with clinical malaria (*i.e.* positive *Plasmodium* RDT and ≥38 °C ear temperature) or severely anemic in combination with a positive RDT result. Iron supplementation will be offered to severely anemic individuals with a negative RDT result.

To avoid interference of potential on-going control programs against helminthiases with the infection status of the trial participants, communication with local stakeholders will be established to ascertain that trial participants will not undergo MDA treatment. Missed-out rounds of planned MDA against helminthiases in study participants will be substituted with a free single-dose treatment (*i.e.* albendazole 400 mg + ivermectin 200 µg/kg) against STH, *S. stercoralis* as well as *Filaria* infection at the study endpoint (after the day 360 follow-up assessment) offered by the study team. At each follow-up time point, participants will be interviewed whether they had taken any anthelmintic treatment (e.g. self-purchased, obtained from clinics etc).

5.6 Concomitant therapy

All medications taken one month before and during the study period until the last stool examination must be recorded with indication, dose regimen, date and time of administration.

Medication(s)/treatment(s) permitted during the trial:

- Analgesics and antipyretics are allowed to be given to the subjects in case of fever, antiemetics to prevent nausea and vomiting and/or antibiotics to prevent or treat bacterial superinfection.

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

- No other active drugs against helminths are permitted during the trial.

- No drugs with known interactions with the study medication are permitted during the trial.

6. Safety assessments

Few AEs have been reported following ivermectin-albendazole co-administration in STH-infected individuals. The most common AEs were abdominal cramps, headache, fatigue, nausea, diarrhea, fever and vertigo [7, 8, 34].

The safety profile of co-administered ivermectin and albendazole will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs and a physical, clinical and biochemical examinations.

6.1 Adverse event definitions

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

a) Any unfavorable and unintended signs, symptoms or disease temporally associated with the use of a medicinal product, whether or not considered related to the condition under study and the study product;

b) Any abnormality detected during physical examination.

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

The observation time for AEs starts when the treatment is initiated until day 21 (3 weeks after last drug administration).

These data will be recorded on the appropriate case report form (CRF) sections, regardless of whether they are thought to be associated with the study or the drug under investigation. Associated with the use of the drug means that there is a reasonable possibility that the event may have been caused by the drug (see also relatedness definitions below).

6.1.1 Severity grading

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

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

6.1.2 Relatedness

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

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

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

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

6.1.3 Expectedness

Expected adverse drug reaction: Any AE possibly related to the co-administration of ivermectin-albendazole reported in the literature or on the drug package leaflets and listed in the consent form.

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

6.1.4 Serious adverse events

According to the ICH "Clinical Safety Data Management: Definitions and standards for expedited Reporting E2A" [35], a serious adverse event (SAE) includes any event (experience) or reaction in any untoward medical occurrence that at any dose:

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

A "severe" AE does not necessarily meet the criteria for a "serious" AE. SAEs are reported from consent to 3 weeks post-treatment (Day 21).

SAEs that are still ongoing at the end of the study period will be followed up to determine the final outcome.

The causality of any SAE that occurs after the study period and its possible relatedness to the study treatment or study participation will also be assessed by investigators as described in section 6.1.2.

6.1.5 Suspected unexpected serious adverse reactions

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

6.2 Methods of recording and assessing adverse events

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, physical and biochemical 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 also be interviewed 3 and 24 hours and again 3 weeks after treatment about the occurrence of AEs (see chapter 4.6).

Information on all AEs (onset, duration, intensity, seriousness and causality) will be immediately entered in the appropriate AE module of the CRF that serves as 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 and iii) an assessment of intensity of AEs will be judged by the study physician.

All SAEs or SUSARs must be reported as described in Section 6.3.

6.3 Reporting of serious adverse events

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

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

6.4 Safety reporting to Health Authorities and 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 'Ethikkomission Nordwest- und Zentralschweiz' (EKNZ, Switzerland), the ethics committee and the 'Direction de la Pharmacie, du Médicament et des Laboratoires (DPML)' in Côte d'Ivoire according to national rules. Fatal or life-threatening SAEs or SUSARs will be reported within 24 hours followed by a complete report within 7 additional calendar days. Other SAEs and SUSARs that are not fatal or life-threatening will be filed as soon as possible but no later than 14 days after first knowledge by the sponsor.

7. Statistics

7.1 Definition of primary endpoint

CR of co-administered ivermectin-albendazole against *T. trichiura* is the primary endpoint in our study. Since treatment success is influenced by infection intensity, stratified block randomization will be used (baseline infection intensity: light infections and moderate/heavy infections) to ensure balanced treatment groups in terms of infection intensity.

7.2 Justification of number of trial subjects

Parallel group multi-country study

Based on available summarized efficacy measures from a recent review [1] and the published literature, we assume that the CR of albendazole against *T. trichiura* is 30% compared to 50% in the albendazole-ivermectin treatment regimen. To detect a difference with 90% power at a two-sided 5% significance level, we require 121 participants per study arm and 143 to account for potential loss to follow-up of 15%. We further assume the same treatment efficacy in the mid-term treatment and a 6-months reinfection risk of 10%. Consequently we expect a proportion of negative patients after 12 months of 44% in the albendazole arm and of 65% in the albendazole-ivermectin arm resulting in a required sample size of 111 participants per arm. To account for a loss to follow-up of 30% after 6 months and 40% at final assessment (12 months) we aim to recruit 300 participants in each treatment group (600 in total) in each country.

Subgroup analysis will be conducted stratifying the study population by age category (school-aged and adults). For the subgroup analysis we will pool the data from all 3 countries to ensure sufficient statistical power.

DF study

Since the existence of a drug effect is well known, the main aim of the study is the elucidation of the nature of the dose–response relationship. Modeling approaches showed that with 40 children enrolled in each of the 4 study arms (placebo, 200 µg/kg, 400 µg/kg, and 600 µg/kg co-administered with albendazole (400 mg)) the dose response prediction model had a median precision (one half length of the 95%-confidence intervals) of 10% assuming associated cure rates of 2.5%, 50%, 60% and 70% taking into account a loss to follow up of 10%. The suggested sample size is also in line with the recommendations from *Klingenberg et al. 2009* [36]. This sample size is sufficiently high to determine the key PK parameters as well as pharmacokinetic/pharmacodynamic (PK/PD) relationships taking into account that PK variability is high.

7.3 Description of statistical methods

The primary available case analysis will include all participants with primary end point data. In addition, an intention-to-treat analysis will be conducted considering all participants with missing endpoint data as treatment failure or all as treatment success to ensure that the results are not sensitive to potential loss to follow-up bias. CRs will be calculated as the percentage of egg-positive (larvae- positive for *S. stercoralis*) participants at baseline who become egg-negative (larvae-negative) after treatment. EPG will be assessed by adding up the egg counts from the quadruplicate Kato-Katz thick smears and multiplying this number by a factor of six. For *S. stercoralis* infection no further quantification of larvae in stool will be done. The ERR of STH infection will be calculated as:

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

In the primary model we estimate the difference among CRs by using unadjusted logistic regressions. In a subsequent analysis an adjusted logistic regression (adjustment for age, sex and weight) will be performed.

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

Results from the stool RDT for fecal occult blood will be categorized as negative, trace and positive. For calprotectin, individuals with levels exceeding 50 µg/g will be considered as positive and concentrations be classified into low (51–149 µg/g), medium (150–299 µg/g) and high (≥300 µg/g) intensity [16].

Anthropometric measurements such as height and weight of school-aged children will be translated into weight-for-age, height-for-age and weight-for-height related z-scores using readily available Stata macros calculating growth indicators for children 5-19 years [37]. Body mass index and indicators for muscle and fat tissue such as MUAC and skinfold thickness will serve as additional indicators of nutritional status for adults and will further be classified using a percentiles approach to compare within populations [38].

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 [25].

Nutritional and morbidity indicators will be analysed using logistic and linear regression as appropriate. To compare individual's changes in nutrition/morbidity categories as an effect from treatment McNemar's test will be applied. The analysis after 6 and 12 month of follow-up will be complemented by generalized estimating equation (GEE) models with independent correlation structure and empirical estimators to account for missing data.

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

On the basis of the LC-MS/MS measurements, the following PK parameters for plasma 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 infinity

$T_{1/2}$ elimination half-life

T and AUC above minimal inhibitory concentration (MIC)

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.

Further PK analysis will be undertaken fitting a structural compartmental PK model with the software NONMEM 7 [39] via nonlinear mixed effects modeling (allowing for both between patient variation and random effects). This model will describe the plasma drug levels in time, allowing one to investigate variation between patients in drug levels. In addition, PK/PD analysis will be undertaken via NONMEM to investigate the drivers of cure and/or burden reduction and potentially any covariates with drug levels.

7.4 Description of data management and data quality control

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

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

1. Eggs counts of *T. trichiura*, *A. lumbricoides* and hookworm and infection status with *S. stercoralis* based on participants' stool samples analyzed using the Kato-Katz and Baermann technique, respectively, before (baseline) and at 3 time points after treatment (follow-ups after 3 weeks, 6 and 12 months). Presence of fecal occult blood and elevated calprotectin levels will be evaluated and recorded applying RDTs on the same stool samples and assessment time points.
2. Personal information such as name, age, gender and household composition of trial participants.
3. Anthropometric and clinical characteristics of the trial participants collected using the study's CRF such as weight, height, skinfold thickness, blood pressure, temperature, hemoglobin level, infection status with *Plasmodium spp*. and filariasis, any abnormal medical condition or chronic disease as well as pregnancy in female participants 10 years and above.
4. Number and type of AEs registered in the CRF actively probed for 3 and 24 hours after treatment. The same data will be collected during the collection of the first sample at the 3-week follow-up.
5. Scales for participant-rated treatment satisfaction and self-rated physical functioning in school-aged children captured on different time points (i.e. 3 weeks and 6 months and baseline, 6 and 12 months after treatment, respectively) and recorded on the CRF.
6. Concentration levels of blood and biochemical parameters together with indicators for micronutrient status before (baseline) and at 3 time points after treatment (follow-ups after 3 weeks, 6 and 12 months).
7. Household-level data on socioeconomic characteristics, presence and use of water and sanitation as well as hygiene-related attitudes and practices.

All data on parasitology and questionnaires about AEs, self-reported clinical signs and symptoms, physical functioning, and treatment satisfaction will be paper-captured and subsequently doubled entered (data entry SOP) into ACCESS data entry masks by two independent persons. For quality assurance error, range and consistency checks will be programmed for the ACCESS data entry masks and all double-entered data be cross-checked using the Data Compare utility of EpiInfo. Any discrepancies will be corrected by consulting the hard copy.

Data in category 1 to 6 will be double-entered using an EpiInfo mask and saved in .mdb, .xlsx, .dta, and .csv. Data in category 7 will be directly entered while collecting into tablets using Open Data Kit (free electronic data collection software) and uploaded to a server hosted at Swiss TPH. All categories will be merged into a single master file saved in .dta, .xlsx and .csv. Data will then be analysed as described in section 7.3. Hard copies of the data collected within the trial country such as parasitological, stool RDT, blood parameter sheets and CRFs will remain at Centre Suisse de Recherches Scientifiques en Côte d'Ivoire (CSRS). 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 CSRS. All data is expected to not exceed 5GB.

Invited and screened patients will be listed in a confidential "subject identification list and 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 pseudonymised data and will only be accessible to the local principal investigator. All study-specific data will only contain this unique identifier instead of any names. Electronic data files will be stored on secured network drives with restricted access for study personnel only. Data analysis will be conducted with pseudonymised data and reporting of findings will be fully anonymised. All databases will be password secured.

Essential infrastructure such as lockable cabinets for safe storage of hardcopy data will be made available. Network drives with restricted access for authorized personnel only and appropriate analysis software are available.

8. Duties of the investigator

8.1 Investigator's confirmation

This trial will be conducted in accordance with the protocol, International Conference on Harmonization Good Clinical Practice E6 (R2) (ICH-GCP) and the current version of the Helsinki Declaration.

All protocol modifications must be documented in writing. A protocol amendment can be initiated by either the Sponsor/PI or any Investigator. The Investigator will provide the reasons for the proposed amendment in writing and will discuss with the Sponsor/PI and Co-PIs. Any protocol amendment must be approved and signed by the Sponsor/PI and must be submitted to the appropriate Independent Ethics Committee (IEC) for information and approval, in accordance with local requirements, and to regulatory agencies if required. Approval by IEC must be received before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial 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) and patient liability insurances will be issued in the respective trial countries.

8.3 Project management

The trial team will include the PI (Prof. Jennifer Keiser), three Co-PIs (Dr. Eveline Hürlimann, Dr. Jessica Schulz, and Dr. Jean Coulibaly), a trial statistician (Dr. Jan Hattendorf), as well as a local physician (Dr. Yves Koutouan N'Gbesso), nurses and laboratory technicians. Prof. Jennifer Keiser, Dr. Eveline Hürlimann, Dr. Jessica Schulz and a PhD student will be responsible for staff management, communication with the collaborative group, recruitment monitoring, data management, safety reporting, analysis, report writing and dissemination of the trial results. Dr. Jean Coulibaly and the PhD student will monitor all field activities at the study site. Dr. Yves Koutouan N'Gbesso, will be responsible for patient recruitment, medical aspects of the trial and enrolment of patients in the trial.

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

The study will be submitted for approval by the institutional research commission of the Swiss TPH and the ethics committees of Switzerland (EKNZ: Ethical Commission of northwest/central Switzerland) and Côte d'Ivoire (CNER: Comité Nationale d'Ethique de la Recherche) and the Ivorian medicines regulatory authority (DPML: Direction de la Pharmacie, du Médicament et des Laboratoires). The study will be undertaken in accordance with the Declaration of Helsinki and GCP.

9.2 Evaluation of the risk-benefit ratio

Ivermectin in combination with albendazole are well-known, widely used drugs in mass treatment programs against filariasis, and have little and mainly mild AEs (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 *T. trichiura* will be treated with ivermectin (200 µg/kg)-albendazole (400 mg) considering higher efficacy compared to the existing standard treatment (albendazole monotherapy) and recent inclusion as recommended treatment scheme on the Essentials Medicines List [29].

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 parents or caregivers of eligible children and all adult participants (≥21 years) will be individually informed about benefits and risk associated to the trial. They will have sufficient time for reflection of their child's or their own participation, respectively. 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. In addition to a written informed consent form signed by their parent or caregiver, minor participants (aged 6-20 years) will also be briefed verbally and written assent sought

in form of their name written down or if illiterate by providing a thumb print. Even if the minor participant gives written assent, the parent/caregiver has to sign the consent.

Information sheets are printed in French but will additionally be verbally translated into local languages (*i.e.* Abbé, Attié, Dioula, Moré) during community meetings. To all participants and parents/caregivers 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.

9.4 Subject confidentiality

The obtained data will be handled strictly confidentially. Only members of the study team will have access to the data. Personal data will be coded for data analysis. The codes will be filled with the participant's identity on a separate file (subject identification list and screening log) and stored in a secured place at the local institutions (*i.e.* Côte d'Ivoire: CSRS, Lao PDR: National Institute of Public Health, and Pemba: Public Health Laboratory Ivo de Carneri) and will only be accessible to investigators. 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. 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 include school-aged children, since *T. trichiura* infection occurs often in children; hence this age group is at high risk of infection and is therefore the major target group in MDA campaigns. Pharmacokinetic and DF studies in this population, however, have to our knowledge so far only been done or are underway by the research team itself for the investigated medicine products (*i.e.* ivermectin and albendazole). Since PK parameters vary between children and adults these studies cannot be obtained by carrying out the trial on adults. Our trial will produce more evidence to support the search for a safe and effective treatment scheme against STH infections in children and whole communities.

9.6 Other aspects

Within the DF study one study arm will include school-aged children treated with placebo. However, this group will be treated with a single dose of co-administered albendazole (400 mg) and ivermectin (200µg/kg), as meanwhile listed on the EML of WHO to treat STH infection [29], at the first follow-up (already 3–4 weeks later). 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 3-weeks delay in treatment should not cause any medical concern for the participants of the placebo arm. 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. Quality control and quality assurance

10.1 Monitoring and auditing

We will work with locally based monitors. These will conduct site visits to the investigational facilities for the purpose of monitoring the study. Details will be described in a separate monitoring plan. The investigator will permit them access to study documentation and the clinical supplies dispensing and storage area. Monitoring

observations and findings will be documented and communicated to appropriate study personnel and management. A corrective and preventative action plan will be requested and documented in response to any audit observations. No sponsor initiated audits are foreseen, but audits and inspections may be conducted by the local regulatory authorities or ethics committees. The Investigator agrees to allow inspectors from regulatory agencies to review records and is encouraged to assist the inspectors in their duties, if requested.

10.2 Access to data, handling of data and samples (data protection), archiving (place, duration) and destruction

Information about study subjects will be kept confidential and managed accordingly. A paper 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 results of the research study will be published, but subjects' names or identities will not be revealed. Records will remain confidential. To maintain confidentiality, the Sponsor-Investigator will keep records in locked cabinets and the results of tests will be coded to prevent association with participant's names. Data entered into the ACCESS data entry mask will be accessible only by authorized personnel directly involved with the study and will be encoded. Subject-specific information may be provided to other appropriate medical personnel only with the subject's permission for adults or the parent/caregiver's permission for minors.

After the study has been completed all samples will be destroyed and research data and related material will be kept 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. Storage and backup will be in three places: personal laptops of Jennifer Keiser, Eveline Hürlimann, Jessica Schulz, Chandni Patel and Jean Coulibaly, Swiss TPH shared server and SWITCHdrive (a cloud storage supported by University of Basel). Archiving conditions will be made strictly confidential by password protection.

10.3 Data entered directly in the CRF – definition of source data

Source Data are the clinical findings and observations, laboratory data maintained at the study site. Source data are contained in **source documents**. Local authorities are allowed to access the source data. Data will be entered directly onto the CRFs. The CRF is considered as a source document. All CRFs will be kept for at least 15 years.

The study site will retain the original 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.

10.4 Data and safety monitoring board / data monitoring committee

In our study no data and safety monitoring board will be established, since we work with well-known drugs in a limited number of participants and using a single dose treatment. This study is anticipated to be no greater than minimal risk to participants.

10.5 Study Documents: Translations - Reference language

- 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.

11. Dissemination of results and publication

The final results of this study will be published in a scientific journal and presented at scientific conferences. The Bill & Melinda Gates Foundation will be acknowledged as study funder. All results from this investigation are considered confidential and shall not be made available to any third party by any member of the investigating team before publication. A study report will be shared with the local ethics committees and the national regulatory authorities.

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4. Trial protocol Pemba Island:

Efficacy and safety of ivermectin and albendazole co-administration in school-aged children and adults infected with *Trichuris trichiura*: a multi-country randomized controlled trial

Protocol Number	1		
Version Number	1.01	**Document Date**	13.02.2018
Sponsor Contact	Prof. Dr. Jennifer Keiser, Swiss Tropical and Public Health Institute, Tel.: +41 61 284-8218 Fax: +41 61 284-8105 E-mail: jennifer.keiser@unibas.ch		
Principle Investigator	Prof. Dr. Jennifer Keiser, Swiss Tropical and Public Health Institute, Tel.: +41 61 284-8218 Fax: +41 61 284-8105 E-mail: jennifer.keiser@unibas.ch		
Funding Agency	Bill and Melinda Gates Foundation		

1. General information

I. List of investigators and other persons involved

Title	Names	Institution	Position	Function in trial
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Dr.	Eveline Hürlimann	Swiss TPH	Postdoc	Co-PI
MSc	Shaali Ame	Public Health Laboratory – IdC	Head laboratory Services	Co-PI
MSc	Said Mohammed Ali	Public Health Laboratory - Ivo de Carneri (PHL-IdC), Chake-Chake, Pemba (Tanzania)	CEO	Co-PI
Dr.	Jan Hattendorf	Swiss TPH	Group leader	Statistician

II. Signatures

Statistician

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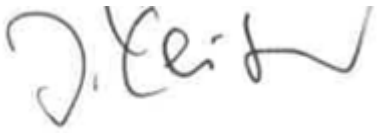
Principal investigator

Signature		Date of Signature 13.02.2018
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Title	Prof.	
Institution	Swiss Tropical and Public Health Institute	
Address	Department of Medical Parasitology and Infection Biology Swiss Tropical and Public Health Institute, Socinstr. 57	
Phone	+41 61 284-8218	

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-Principal investigator

Signature		Date of Signature 13.02.2018
Name	Eveline Hürlimann	
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Institution	Swiss Tropical and Public Health Institute	
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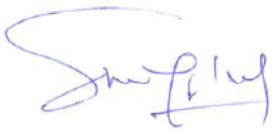
Co-Principal investigator

Signature		Date of Signature 13.02.2018
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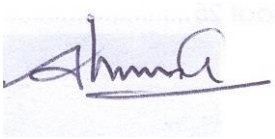
Signature		Date of Signature 13.02.2018
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III. Abbreviations

AE	Adverse event
CI	Confidence interval
CR	Cure rate
CRF	Case report form
EKNZ	Ethikkomission Nordwest- und Zentralschweiz
EML	Essential medicine list
EPG	Eggs per gram
ERR	Egg reduction rate
GCP	Good clinical practice
Hb	Hemoglobin
ICH	International council for harmonization of technical requirements for pharmaceuticals for human use
IEC	Independent ethics committee
MDA	Mass drug administration
MUAC	Mid-upper arm circumference
PC	Preventive chemotherapy
PCR	Polymerase chain reaction
PI	Principal investigator
RDT	Rapid diagnostic test
SAE	Serious adverse event
STH	Soil-transmitted helminth
SUSAR	Suspected unexpected serious adverse reaction
WHO	World Health Organization

IV. Synopsis

Sponsor/Sponsor-Investigator	Prof. Dr. Jennifer Keiser
Study Title	Efficacy and safety of ivermectin and albendazole co-administration in school-aged children and adults infected with *Trichuris trichiura*: a multi-country randomized controlled trial
Short title	Efficacy and safety of IVM/ALB co-administration
Protocol Number, Date and Version	1, 13.02.2018, v1.01
Trial registration	Will be registered on (http://www.controlled-trials.com/)
Clinical phase	Phase 3 trial
Sample size	1800 (600 participants in each of 3 settings)
Indication	*Trichuris trichiura* infection (eggs in stool)
Investigational Product and Reference Treatment	Ivermectin and albendazole
Study Rationale	To provide evidence on potentially enhanced efficacy by combining the standard drug albendazole with ivermectin in school-aged children and adults against infection with *T. trichiura*.
Study Objectives	To compare the efficacy and safety of standard doses of co-administered ivermectin (200 µg/kg) and albendazole (400 mg) compared to albendazole (400 mg) alone in community members aged 6-60 years. Our **primary objective** is to comparatively assess the efficacy in terms of cure rates (CRs) against *T. trichiura* infections among school-aged children and adults of the following oral treatment regimens: • Albendazole (400 mg)/ivermectin (200 µg/kg) combination • Albendazole (400 mg) alone

	The **secondary objectives** of the trial are: a) To evaluate the safety and tolerability of the two treatment regimens b) To evaluate the egg reduction rate (ERR) of the two treatment regimens against *T. trichiura* c) To determine the CRs and ERRs of the drugs in study participants (6-60 years) infected with hookworm, *Ascaris lumbricoides* and *Strongyloides stercoralis* d) To investigate potential extended effects on follow-up helminth prevalences (6 and 12 months post-treatment) of the two treatment regimens (as assessed among participants with cleared infection on days 21 and 180) e) To compare CRs based on egg counts retrieved from novel PCR-based and standard microscopic diagnosis f) To assess potential differences in susceptibility to the two treatment regimen between the hookworm species, *Necator americanus*, *Ancylostoma duodenale* and *A. ceylanicum*, as classified through the novel PCR-based diagnosis g) To characterize *Trichuris* strains from different epidemiological settings h) To evaluate potential benefits from deworming on morbidity indicators (e.g. anemia, occult fecal blood, calprotectin, growth standards, self-reported physical functioning)
Study design	Double blind, randomized controlled trial
Study product / intervention	Administration of a single oral dose of ivermectin + albendazole
Comparator(s)	albendazole (400 mg) alone
Key inclusion / Exclusion criteria	**Inclusion:** School-aged children or adults (6-60 years) infected with *T. trichiura* with at least two slides of the quadruple Kato-Katz thick smears positive and infection intensities of at least 100 eggs per gram of stool (EPG), able and willing to be examined by a study physician at the beginning of the study and to provide two stool samples at baseline and on the three follow-up assessments (approximately 3 weeks, 6 months, and 12 months later), absence of major systemic illnesses or history of chronic disease, written informed consent signed by parents and/or caregivers for minors; and oral assent by school-aged children, no known allergy to study medication, no recent

	anthelminthic treatment (past 4 weeks) and for girls/women of fertile age: not being pregnant or lactating in the 1st week after birth. **Exclusion:** No written informed consent, any abnormal medical conditions or history of acute or severe chronic disease, recent use of anthelminthic drug (past 4 weeks), negative diagnostic or low egg count (less than 100 EPG or less than 2 out of 4 slides positive) result for *T. trichiura*, pregnancy or lactating in the 1st week after birth.
Primary Endpoints	CR on *T. trichiura*
Secondary Endpoints	• ERR against *T. trichiura* • CRs and ERRs against *A. lumbricoides*, hookworm and *S. stercoralis* • Safety • Diagnostic performance • Molecular characterization of *Trichuris* spp. • Changes in morbidity
Exploratory Endpoints	None
Interim Analyses	None
Study Duration	14 months total; up to 12 months per participant
Schedule	06/2018 of first-participant in (planned) 08/2019 of last-participant out (planned)
Study centres	Multinational study with trial sites in Côte d'Ivoire, Lao PDR and Pemba Island (Tanzania)
Measurements & procedures	Two stool samples will be collected if possible on two consecutive days or otherwise within a maximum of 5 days. The medical history of the participants will be assessed with a standardized questionnaire, in addition to a clinical examination carried out by the study physician before treatment. All participants will also be interviewed before treatment, 3 and 24 hours and 3 weeks after treatment about the occurrence of adverse events. Children (6-16 years) will additionally be asked to rate their own physical functioning by replying to a pre-tested questionnaire at baseline and 6 and 12 months after treatment. The efficacy of the treatment and potential extended effects on follow-up prevalence will be determined 14-21 days, 6 months and 12 months post-treatment by collecting another two stool samples. Subjective treatment satisfaction will be assessed 3 hours, 3 weeks and 6 months after treatment to

	investigate relationship with treatment compliance and observed efficacy in reducing egg output and morbidity. All stool samples will be examined with duplicated Kato-Katz thick smears for *T. trichiura*, *A. lumbricoides* and hookworm. *S. stercoralis* infections will be identified using the Baermann technique. For subsequent PCR-analysis a portion of 1.5-2 g of stool from each specimen will be preserved in 70% ethanol and shipped to a reference laboratory. From a subsample of 10 children with heavy intensity infections in each study setting an additional portion of stool (1.5-2 g) will be preserved in 95% ethanol, shipped to a reference laboratory and subjected to whole genome sequencing for characterization of *Trichuris* strains. Fecal occult blood and calprotectin in stool as markers for gut morbidity and inflammation will be detected using a rapid diagnostic test and an immunoassay, respectively. Individuals found positive 6 months after baseline will receive a second round of treatment according to their group scheme. Each participant will be asked to provide a finger-prick blood sample for hemoglobin measurement and co-infection with *Wuchereria bancrofti* at baseline and 6 and 12 months after treatment. At the same time points anthropometric measurements (i.e. height, weight, mid-upper arm circumference (MUAC) and skinfold thickness) will be taken for all participants. To all participating households, a questionnaire will be administered assessing information on socioeconomic characteristics and access to sanitation, water facilities, and hygiene behavior.
Statistical Analyses	An available case analysis 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 egg-positive subjects at baseline who become egg-negative after treatment. Differences among CRs (between treatment arms and between diagnostic approaches) will be analysed by using crude and adjusted logistic regression modelling (adjustment for age, sex, community, weight and height). Geometric and arithmetic mean egg counts will be calculated for the different treatment arms before and after treatment to assess the corresponding ERRs. Bootstrap resampling method with 5,000 replicates will be used to calculate 95% confidence intervals (CIs) for ERRs. Morbidity indicators (continuous measurements) will be compared in a first step within and between groups using independent and paired t-test statistics while chi-square testing will be performed for binary/categorical outcomes (e.g. anemia, blood in stool). To compare individual's changes in morbidity categories as an effect from treatment McNemar's test will be applied. In a second step, adjusted repeated measures linear and logistic regressions using generalized estimating equation (GEE) models will be performed to assess development of morbidity indicators within each individual and related factors be investigated.
GCP statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ICH-GCP E6 (R2) as well as all national legal and regulatory requirements.

Key explanation for the inclusion of children	This study will involve school-aged children, since an infection with *T. trichiura* occurs most often in children and they are further the main target group of deworming campaigns.
Recruitment procedure	The longitudinal trial will be conducted as a multi-country study with two settings in Africa and one in Asia recruiting each 600 community members: • West African setting: Côte d'Ivoire • East African setting: Pemba (Zanzibar, Tanzania) • Asian setting: Lao PDR The studies will be conducted in areas with moderate to high *T. trichiura* infection intensities (communities with a prevalence ≥ 25%) identified from earlier studies and/or based of experience of the local collaborating teams. They will be implemented as community-based studies in order to recruit participants from a broad age range (6-60 years). Ideally, entire communities with a population size of < 1000 inhabitants will be included in the study for pre-screening and identification of *T. trichiura* cases to avoid potential selection bias of households.
Coverage of damages	Winterthur Police Nr. 4746321, National Insurance Corporation of Tanzania (to be issued)
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.

2. Background information

Albendazole and mebendazole are the most widely used drugs for preventive chemotherapy (PC) campaigns against soil-transmitted helminth (STH) infections. Albendazole is characterized by high cure rates (CRs) and egg reduction rates (ERRs) against infections with *Ascaris lumbricoides* (95.6% and 98.5%) and hookworm infections (79.4 and 89.6%). Lower efficacy is observed against *Trichuris trichiura* infections (CR 31.5%, and ERR of 49.8%) [1].

Therapies combining two or more drugs are widely advocated in different therapeutic areas such as tuberculosis, malaria, HIV/AIDS or cancer. The underlying rationale for multifactorial pharmacological treatment varies with the disease and includes the protection against the selection of drug-resistance, and hence, a prolongation of the life-span of effective and available drugs, and to increase and broaden the efficacy over drugs being administered in mono-therapy [2].

A recent review and meta-analysis found that ivermectin co-administered with albendazole is highly efficacious for the treatment of *T. trichiura* and is comparatively more efficacious than albendazole alone (Figure 1) [3]. Efficacy of ivermectin and albendazole against *A. lumbricoides* and hookworm are comparable and in some cases more efficacious than albendazole alone. Summarized efficacy measures of albendazole, mebendazole, and ivermectin against trichuriasis from a recent review [1] and earlier trials [4, 5] are shown in Table 1.

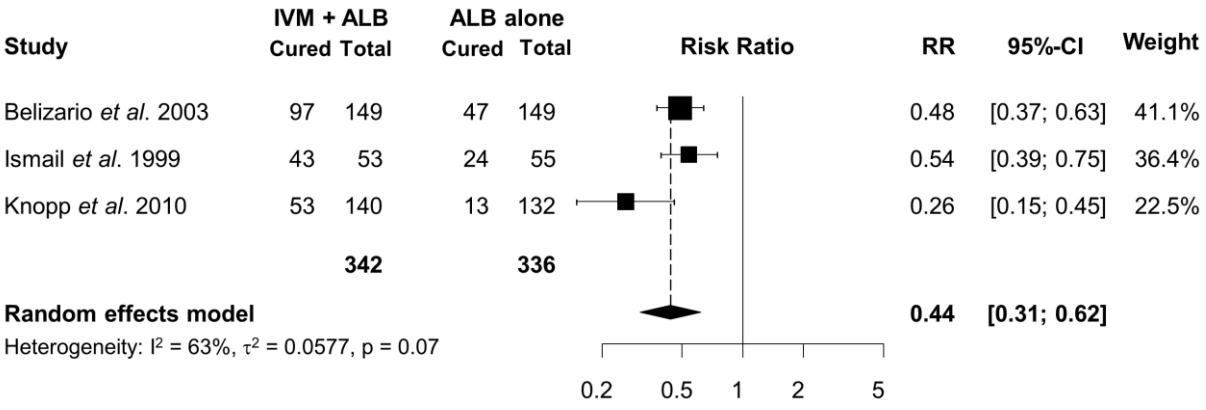

Figure 1. Forest plot displaying the results of a random-effects meta-analysis of the effect of the co-administration of albendazole-ivermectin on the number of patients infected with *T. trichiura* compared to albendazole alone.

Table 1. Average CRs and ERRs of albendazole and mebendazole for *T. trichiura* from a recent review [6] as well as findings from studies investigating ivermectin [4, 5]

Drug	CR (%)	95% CI	ERR (%)	95% CI
Albendazole	30.7	(21.0, 42.5)	49.9	(39.0, 60.6)
Mebendazole	42.1	(25.9, 60.2)	66.0	(54.6, 77.3)
Ivermectin	11-35	NA	43-98	NA

The individual studies included in the review are summarized in Table 2. All four studies are randomized controlled trials and used the standard dose of 200 µg/kg ivermectin and 400 mg albendazole [4, 7-9]. Against infections with *T. trichiura*, CRs ranging from 27.5-81.1%, ERR based on geometric mean ranging from 91.3-99.7%, and ERR based on arithmetic mean ranging from 85.6-97.5% were observed. CRs for *T. trichiura*

observed in Asian settings were higher than in African settings. One reason for this finding may be differences in the study design and quality (e.g., in terms of diagnostic approach used). Another possible reason recently highlighted is genetic diversity of *T. trichiura* strains and variation in susceptibility to anthelmintics and/or drug resistance [10-12]. Interestingly, the higher efficacy of ivermectin in combination with albendazole translated – at least in some settings – into lower prevalences even after one year [4, 13]. The efficacy of albendazole-ivermectin against *A. lumbricoides* was excellent (CRs >78% and ERRs >99.5%), while moderate CRs (50-66.7%) and high ERRs (>95.4%) were observed against hookworm.

Table 2. Known efficacy of co-administered ALB-IVM$^{\Psi}$ against *T. trichiura*:

Study	**Setting**	**Cure rate in % (n_{neg}/n)**	**Eggs per gram (pre/post)**	**Egg reduction rate in %**
Ismail et al. 1999	Sri Lanka	81.1% (43/53)	1544.0/78.7 (unkwn)	94.9% (unkwn)
Belizario et al. 2003	Philippines	65.1% (97/149)	4948.1/122.5 (ar) 550.0/1.9 (geo)	97.5% (ar) 99.7% (geo)
Knopp et al. 2010	Tanzania (Pemba)	37.9% (53/140)	127/11 (geo)	91.3% (geo)
Speich et al. 2015	Tanzania (Pemba)	27.5% (30/109)	1059/153 (ar) 489/27 (geo)	85.6% (ar) 94.5% (geo)
All studies		**49.4% (223/451)**		

$^{\Psi}$*Considered doses: albendazole=400 mg, ivermectin=200 µg/kg*

ar=arithmetic mean, geo=geometric mean, unkwn=unknown mean

The WHO Expert Committee met from March 27-31, 2017 and, based on review of the dossier, made the following recommendation:

"…adding ivermectin on the Essential Medicines List under the section intestinal anthelminthic for use against Strongyloides stercoralis and STH. It may be used in combination with albendazole for treatment of soil-transmitted helminthiasis."

This important milestone paves the way for further, standardized trials to evaluate the efficacy of this combination among school-aged children in a range of epidemiological settings. In addition, the combination should be evaluated among adults, as there is growing interest in broadening deworming to include adults in order to move from morbidity control toward interruption of transmission [14, 15].

In the proposed work, three trials are planned across a range of transmission settings, including Côte d'Ivoire, Lao PDR, and Pemba (Tanzania). Follow-up will be conducted at 1, 6, and 12 months to inform treatment frequency. Results from these trials will inform decisions on how the combination could be introduced into existing MDA programs and therefore provide a valuable adjunct tool for interrupting STH transmission.

3. Trial objective and purpose

The overall goal of the study is to assess the efficacy and safety of co-administered albendazole and ivermectin versus albendazole alone (standard of care) against *T. trichiura* infections in children and adults (6-60 years) in different transmission settings and geographies.

We hypothesize that albendazole-ivermectin has a higher efficacy against *T. trichiura* infections than albendazole alone, and hence, the efficacy against all three commonly STH species (*A. lumbricoides*, *T. trichiura*, and hookworm) and *Strongyloides stercoralis* will be increased.

The **primary objective** of the trial is to comparatively assess the efficacy in terms of CR against *T. trichiura* infections among school-aged children and adults from three different epidemiological settings and monitored over a 12-month period of the following two oral treatment regimens:

- Albendazole/ivermectin combination
- Albendazole alone

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

a) To evaluate the safety and tolerability of the treatment regimens
b) To evaluate the ERR of the treatment regimens against *T. trichiura*
c) To determine the CRs and ERRs of the drugs in study participants (6-60 years) infected with hookworm, *Ascaris lumbricoides* and *Strongyloides stercoralis*
d) To investigate potential extended effects on follow-up helminth prevalences (6 and 12 months post-treatment) of the two treatment regimens (as assessed among participants with cleared infection on days 21 and 180)
e) To compare CRs based on egg counts retrieved from novel PCR-based and standard microscopic diagnosis
f) To assess potential differences in susceptibility to the two treatment regimen between the two hookworm species, *Necator americanus*, *Ancylostoma duodenale* and *A. ceylanicum*, as classified through the novel PCR-based diagnosis
g) To characterize *Trichuris* strains from different epidemiological settings through genotyping
h) To evaluate potential benefits from deworming on morbidity indicators (clinically evaluated and self-rated from questionnaire interviews)

4. Methodology

4.1 Primary and secondary endpoint

CR (primary end point, *i.e.* conversion from being egg positive pre-treatment to egg negative post-treatment) and ERR (secondary end point). In addition, diagnostic performance using different tools will be evaluated, *Trichuris* strains described using molecular characterization and safety and potential benefits on morbidity indicators from treatment assessed (secondary end points).

4.2 Type of trial

Double blind randomized controlled trial.

4.3 Trial design

4.3.1 Baseline survey and screening

A randomized-controlled trial will be conducted with two treatment arms to be followed-up over a 12 months period with an intermediate re-treatment of participants found re-infected after 6 months (Figure). This trial will be conducted as a multi-country study; thus, in each setting a separate trial according to the design described below will be set up, to provide a better basis for the subsequent generalization of its findings. This arises from the possibility of recruiting the subjects from a wider population and of administering the medication in a broader range of clinical settings, thus presenting an experimental situation that is more typical of future use. The study includes one baseline and three follow-up assessments at 3 weeks (day 21), 6 months (day 180), and 12 months (day 360).

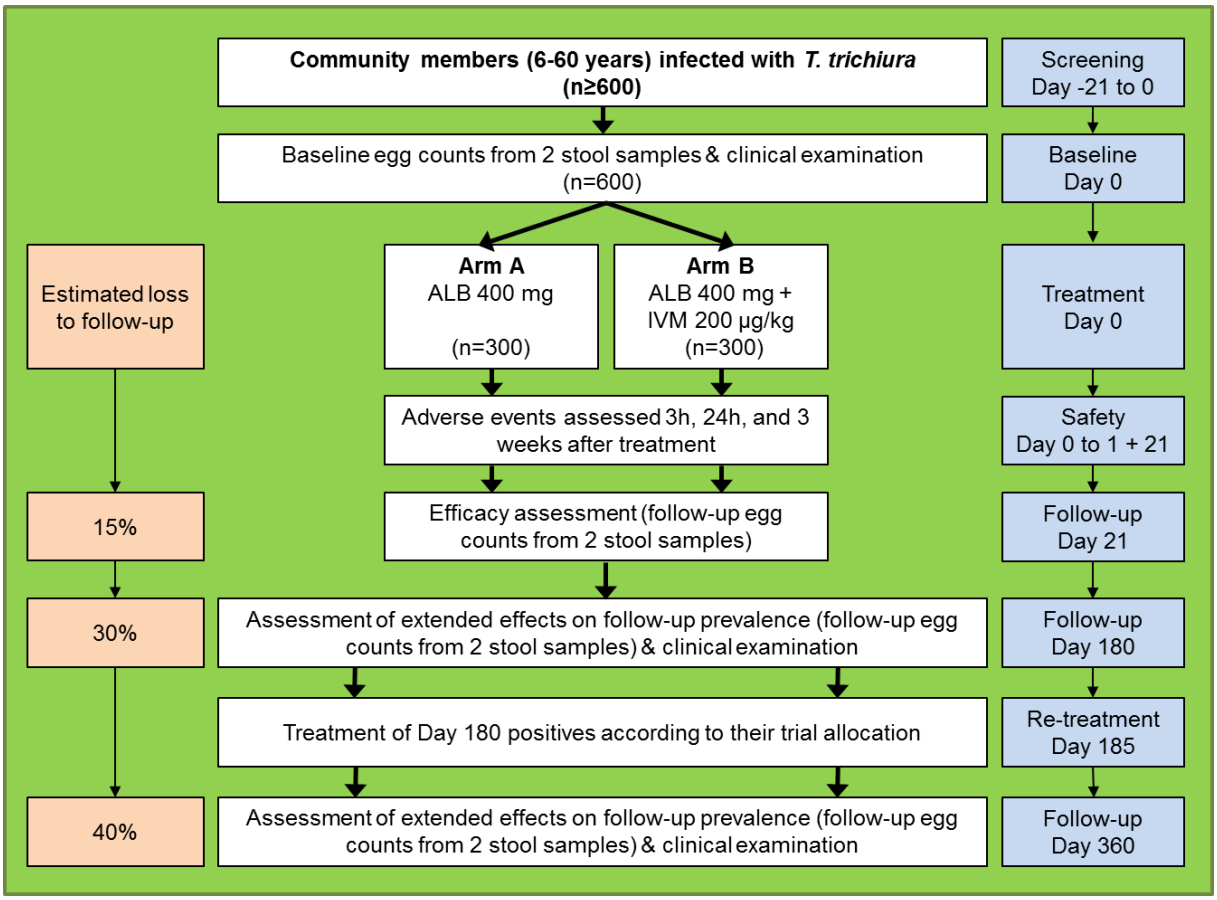

Figure 1. Design and timeline of the randomized-controlled trial to be implemented in each of three settings.

The study is designed as a two-armed trial including one arm with a single drug administration (arm A; albendazole) and one arm with combined treatment through co-administration of separate tablets (arm B; albendazole and ivermectin).

The trial will be conducted as a multi-country study with two settings in Africa and one in Asia, namely Côte d'Ivoire, Pemba (Zanzibar, Tanzania) and Lao PDR.

At baseline, all participants will be asked to provide two stool samples (within a maximum of 5 days). From each stool specimen, duplicate Kato-Katz thick smears (41.7 mg each) [16] will be prepared and read under a

microscope for eggs of *T. trichiura*, *A. lumbricoides* and hookworm by experienced technicians and a subsequent independent quality control of sample results (approximately 10%) will be conducted. Results are considered correct if the following tolerance margin is not exceeded: (i) No difference in presence/absence of hookworm, *A. lumbricoides* and *T. trichiura*, (ii) egg counts are +/-10 eggs for counts ≤100 eggs or +/-20% for counts >100 eggs (for each species separately) [17]. 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 count per gram of stool (EPG) will be calculated for each treatment arm. All microscopically analyzed quadruplicate Kato-Katz thick smears will be destroyed within one day (after passing the quality control). *S. stercoralis* infections will be identified using the Baermann technique. Additionally, a portion of 1.5-2 g of stool from each specimen will be preserved in 70% ethanol and shipped to a reference laboratory for polymerase chain reaction (PCR) analysis [18]. PCR will allow to accurately determining efficacy and for further classification of hookworm infection into the three species *N. americanus, A. duodenale* and *A. ceylanicum*. From a subsample of 10 children with heavy intensity infections an additional portion of stool (1.5-2 g) will be preserved in 95% ethanol, shipped to a reference laboratory and subjected to whole genome sequencing for characterization of *Trichuris* strains. Each collected stool sample will further be tested on fecal occult blood and calprotectin as proxies for gut morbidity and inflammation using a rapid diagnostic test and an immunoassay, respectively [19]. The same sampling procedure and diagnostic approach will be applied at days 21, 180 and 360 post-treatment.

Patients with filarial disease showed significantly higher numbers of adverse events (AEs) for treatment with ivermectin in combination with albendazole in earlier studies [20-22]. A rapid diagnostic test (RDT; i.e., SD BIOLINE Oncho/LF IgG_4 biplex test) to detect antigens in the blood will therefore be used to identify potential co-infection with *Wuchereria bancrofti*.

A clinical examination of the study participants assessing general health, anthropometric parameters including height, weight, mid-upper arm circumference (MUAC) and triceps skinfold thickness as well as tympanic temperature using an ear thermometer will precede the treatment and will be repeated on two follow-up assessments (days 180 and 360) to evaluate potential benefits from deworming. Each participant will be asked to provide a finger-prick blood sample to evaluate hemoglobin (Hb) levels using a HemoCue analyzer (Hemocue Hb 301 system; Angelholm, Sweden) following the same (re-)assessment schedule. To avoid accidental treatment of pregnant girls/women all female participants (≥ 10 years) will be asked to provide a urine sample to be subjected to a pregnancy RDT on day 0 and day 180.

All trial participants will further be asked about existing clinical symptoms before drug administration. Additionally, they will be asked to provide subjective short-term (e.g. convenience of treatment) and long-term (e.g. effectiveness in reducing symptoms) treatment satisfaction embedded in the re-assessment questionnaires. As a measure of patient-rated physical functioning and wellbeing all children (6-16 years) will be administered a questionnaire before, 6 and 12 months after treatment, based and adapted from tools already validated in school-aged children from rural settings in Côte d'Ivoire [23]. Before application this tool will be adapted to local conditions of Pemba and pre-tested in a comparable school-aged population not otherwise involved in this trial. To adjust for known influencing factors with regard to reinfection and morbidity [24, 25] in the subsequent analysis and to identify risk factors for residual infections [26] a household-based questionnaire will be administered to one adult member of each participating household, assessing information on socioeconomic characteristics, access to sanitation and water facilities as well as hygiene behavior.

4.3.2 Assessment of efficacy after treatment

The efficacy of the treatment will be determined 21 days post-treatment by collecting another two stool samples which will be microscopically examined for *T. trichiura* using duplicate Kato-Katz thick smears and potential co-infection with *S. stercoralis* applying the Baermann technique. Participants will be considered *T. trichiura* cured if no eggs have been found in the stool. EPG will be assessed by adding up the egg counts from the quadruplicate Kato-Katz thick smears and multiplying this number by a factor of six. Geometric and arithmetic mean egg counts will be calculated for the different treatment arms before and after treatment to assess the

corresponding ERRs. The stool samples collected 21 days post-treatment for efficacy assessment will further be re-tested with the same rapid diagnostic test and immunoassay used at baseline to determine fecal occult blood and calprotectin levels. Frequencies of subjects found positive with either of the two markers and by intensity category for calprotectin will be calculated by treatment arm.
At the end of the study (approximately 12 months post-treatment) all participants remaining positive for *T. trichiura* and other soil-transmitted helminths will be treated with albendazole-ivermectin, the currently best recommended treatment against *T. trichiura*.

Potential extended effects on follow-up helminth prevalences will be assessed using the same methodological approach as used for the efficacy assessment and will be based on stool samples collected 6 and 12 months post-treatment. Likewise fecal occult blood and calprotectin will be re-determined on the same stool samples.

To assess eventual reduction in morbidity indicators all trial participants will be asked to provide another finger-prick blood sample at the 6 and 12 month follow-up for Hb measurement. Anthropometric measurement including height, weight, MUAC and triceps skinfold thickness will be repeated on the same occasion. Children (6-16 years) will be asked to re-assess their own physical functioning in repeated questionnaire interviews during these two last follow-ups. Long-term satisfaction with the treatment will be asked 6 months past-treatment. Mean values for continuous outcomes and frequencies for binary/categorical outcomes will be calculated for each treatment arm and follow-up time point and compared using descriptive and repeated measurement analysis as detailed in section 7.3.

4.4 Measure to minimize bias

Study participants eligible for treatment will be randomly assigned to one of the two treatment arms using a computer-generated stratified block randomization code. The random allocation sequence with varying random blocks of four or eight and stratified by 2 levels of baseline infection intensity (light: <1000 EPG, and moderate plus heavy: ≥ 1000 EPG *T. trichiura* infections) will be provided by a statistician. The treatment arms will have an equal number of participants with light infection intensity, although the number of light versus moderate/heavy infections are not expected to be equal in each arm, depending on the distribution of infection intensity in the recruited cohort. The study will be double blinded.

4.5 Study duration and duration of subject participation

The trial will last fourteen months. The screening for the baseline will start three weeks prior to the treatment. Follow-up screening will take place 14-21 days, 180 days and 360 days post-treatment and last each time for about three weeks. Schedules of visits are summarized below.

4.6 Schedule of visits

Table 1. Schedule of visits of longitudinal study.

	Screening -21 to -1 days	**Baseline/Treatment/Safety** Hours			**Follow up** Days			
		0		3	24	21	180	185	360
Diagnosis (stool examination)	X		**Randomization and treatment**			X	X	**Selective re-treatment**	X
Gut morbidity (stool RDTs)	X					X	X		X
Informed consent	X								
Demographics	X								
Medical history		X							
Clinical examination		X					X		X
Pregnancy testing		X					X		
Hemoglobin measurement		X					X		X
***W. bancrofti* co-infection**		X					X		X
Physical functioning		X					X		X
Capturing AEs				X	X	X			
Capturing SAE				X	X	X			
Treatment satisfaction				X		X	X		

5. Selection of the trial subjects

5.1 Recruitment

The study will be carried out in community members aged 6–60 years in areas with moderate to high *T. trichiura* infection intensities (communities with a prevalence ≥ 25%) identified from earlier studies and/or based of experience of the local collaborating teams. The trial will be implemented as community-based study in order to recruit participants from a broad age range (6–60 years). Ideally, entire communities with a population size of < 1000 inhabitants will be included in the study for pre-screening and identification of *T. trichiura* cases to avoid potential selection bias of households. Another option might be to run the trial at schools and invite school-aged children and one adult for each child of the same household.

All adult community members, including parents/caregivers of minor participants, will be invited to participate in an information meeting to explain the purpose and procedures of the study, including potential benefits and risks. Parents/caregivers/potential participants will be encouraged to ask questions in an open discussion forum. During this session, they will be informed of preventive actions they can take to help protect their children from

acquiring *T. trichiura* and other STH infections in the future (e.g., adequate food preparation and defecation behavior).

Those parents/caregivers and their children 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. Written informed consent signed by either the participant him/herself (≥18 years of age) or by parents and/or caregivers for children; and oral assent by child (aged 6–17 years).
2. Agree to comply with study procedures, including provision of two stool samples at the beginning (baseline) and on three follow-up assessments (approximately 3 weeks, 6 months, and 12 months later).
3. Aged ≥6 to ≤60 years.
4. At least two slides of the quadruple Kato-Katz thick smears positive for *T. trichiura* and infection intensities of at least 100 eggs per gram of stool (EPG).

5.3 Exclusion criteria

1. No written informed consent by individual/parents and/or caregiver.
2. Presence of major systemic illnesses, e.g., severe anaemia (below 80 g/l Hb according to WHO)[27], as assessed by a medical doctor, upon initial clinical assessment.
3. History of acute or severe chronic disease (*e.g.* cancer, diabetes, chronic heart, liver or renal disease).
4. Recent use of anthelmintic drug (within past 4 weeks).
5. Attending other clinical trials during the study.
6. Negative or low egg count (less than 100 EPG or less than 2 out of 4 slides positive) diagnostic result for *T. trichiura* eggs in the stool.
7. Pregnancy or lactating in the 1st week after birth (according to WHO guidelines within LF control programs [28]).
8. Known allergy to study medications (*i.e.* albendazole and ivermectin).

5.4 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 a participant withdraws).

2. At the discretion of the Principal Investigator (PI) or co-PI, if the participant is not compliant to the requirements of the protocol.

Discontinued 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 (adverse events monitoring) will be conducted.

5.5 Treatment of subjects

All *T. trichiura*-infected, consenting, and participating community members will be treated with the respective single or combination treatment regimen at day 0. 400 mg albendazole will be the product of Glaxo Smith Kline (Zentel®) and a single tablet administered. 3 mg tablets of ivermectin will be obtained from Merck (Stromectol®). The weight will be recorded for each participant and the correct dose evaluated and administered. Matching ivermectin placebo tablets will be produced by the University of Basel, Switzerland. To ensure double-

blinding the tablets will be repacked into neutral separate plastic bags each containing one albendazole tablet and the maximum number of ivermectin tablets with regard to weight and dose or the corresponding number of placebo tablets. Since albendazole and ivermectin are known to be better absorbed in humans after a high-fat meal was consumed, participants will receive a local high-fat breakfast (sandwich with *e.g.* oily sardines) prior to treatment [29, 30].

All drugs will be administered in the presence of the investigator(s), 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. The Principal Investigator 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.

To avoid interference of potential on-going control programs against helminthiases with the infection status of the trial participants, communication with local stakeholders will be established to ascertain that trial participants will not undergo MDA treatment. Missed-out rounds of planned MDA against STH in the participating study communities be substituted with a free community-wide single-dose treatment (i.e., albendazole 400 mg + ivermectin 200 µg/kg) against STH as well as *S. stercoralis* infection at the study endpoint (after the day 360 follow-up assessment) offered by the study team. At each follow-up time point, participants will be interviewed whether they had taken anthelmintic treatment (e.g. self-purchased, obtained from clinics etc). Participants found to be severely anemic at any of the three assessment time points (baseline, 6 and 12 months post-treatment) will be referred to the next hospital/clinic.

5.6 Concomitant therapy

All medications taken one month before and during the study period until the last stool examination must be recorded with indication, dose regimen, date and time of administration.

Medication(s)/treatment(s) permitted during the trial:

- Analgesics and antipyretics are allowed to be given to the subjects in case of fever, antiemetics to prevent nausea and vomiting and/or antibiotics to prevent or treat bacterial superinfection.

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

- No other active drugs against helminths are permitted during the trial.

6. Safety assessments

Few AEs have been reported following ivermectin-albendazole co-administration in STH-infected individuals. The most common AEs were abdominal cramps, headache, fatigue, nausea, diarrhea, fever and vertigo [8, 9, 31]. The safety profile of co-administered ivermectin and albendazole will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs and a physical and clinical examination.

6.1 Adverse event definitions

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

a) Any unfavorable and unintended signs, symptoms or disease temporally associated with the use of a medicinal product, whether or not considered related to the condition under study and the study product;

b) Any abnormality detected during physical examination.

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

The observation time for AEs starts when the treatment is initiated until day 21 (3 weeks after last drug administration).

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

6.1.1 Severity grading

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

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

6.1.2 Relatedness

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

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

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

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

6.1.3 Expectedness

Expected adverse drug reaction: Any AE possibly related to the co-administration of ivermectin-albendazole reported in the literature or on the drug package leaflets and listed in the consent form.

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

6.1.4 Serious adverse events

According to the ICH "Clinical Safety Data Management: Definitions and standards for expedited Reporting E2A" [32], a serious adverse event (SAE) includes any event (experience) or reaction in any untoward medical occurrence that at any dose:

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

A "severe" AE does not necessarily meet the criteria for a "serious" AE. Serious AEs are reported from consent to 24 hours post-treatment (Day 2).

SAEs that are still ongoing at the end of the study period will be followed up to determine the final outcome.

The causality of any SAE that occurs after the study period and its possible relatedness to the study treatment or study participation will also be assessed by investigators as described in section 6.1.2.

6.1.5 Suspected unexpected serious adverse reactions

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

6.2 Methods of recording and assessing adverse events

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 and physical 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 also be interviewed 3 and 24 hours and again 3 weeks after treatment about the occurrence of AEs (see chapter 4.6).

Information on all AEs (onset, duration, intensity, seriousness and causality) will be immediately entered in the appropriate AE module of the case report form (CRF) that serves as 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 and iii) an assessment of intensity of AEs will be judged by the study physician.

All SAEs or SUSARs must be reported as described in Section 6.3.

6.3 Reporting of serious adverse events

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

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Within the following 48 hours, the local co-investigator must provide to study sponsor-investigator further information on the SAE or the unanticipated problem in the form of a written narrative. This should include a copy of a completed SAE form, and any other diagnostic information that will assist the understanding of the event. In exceptional circumstances, a SAE may be reported by telephone. In these cases, a written report must

be sent immediately thereafter by fax or e-mail. Names, addresses and telephone for SAE reporting will be included in the trial-specific SAE form. Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant medications).

6.4 Safety reporting to Health Authorities and 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 'Ethikkomission Nordwest- und Zentralschweiz' (EKNZ, Switzerland), and the 'Zanzibar Medical Research and Ethical Committee' (ZAMREC, Tanzania) in Zanzibar according to national rules. Fatal or life-threatening SAEs or SUSARs will be reported within 24 hours followed by a complete report within 7 additional calendar days. Other SAEs and SUSARs that are not fatal or life-threatening will be filed as soon as possible but no later than 14 days after first knowledge by the sponsor.

7. Statistics

7.1 Definition of primary endpoint

Cure rate of co-administered ivermectin-albendazole against *T. trichiura* is the primary endpoint in our study. Since this might be influenced by infection intensity, treatment groups will be equally balanced in terms of infection intensity by 2 levels of baseline infection intensity (light infections and moderate/heavy infections).

7.2 Justification of number of trial subjects

Based on available summarized efficacy measures from a recent review [1] and the published literature, we assume that the CR of albendazole against *T. trichiura* is 30% compared to 50% in the albendazole-ivermectin treatment regimen. To detect a difference with 90% power at a two-sided 5% significance level, we require 121 participants per study arm and 143 to account for potential loss to follow-up of 15%. We further assume the same treatment efficacy in the mid-term treatment and a 6-months reinfection risk of 10%. Consequently we expect a proportion of negative patients after 12 months of 44% in the albendazole arm and of 65% in the albendazole-ivermectin arm resulting in a required sample size of 111 participants per arm. To account for a loss to follow-up of 30% after 6 months and 40% at final assessment (12 months) we aim to recruit 300 participants in each group (600 in total). This number is largely sufficient to further show differences in efficacy in subgroups such as school-aged versus adult study populations without losing statistical power as long as individuals get recruited in similar proportions to these two groups.

7.3 Description of statistical methods

The primary available case analysis will include all participants with primary end point data. In addition, an intention-to-treat analysis will be conducted considering all participants with missing endpoint data as treatment failure or all as treatment success to ensure that the results are not sensitive to potential loss to follow-up bias. CRs will be calculated as the percentage of egg-positive children at baseline who become egg-negative after treatment. EPG will be assessed by adding up the egg counts from the quadruplicate Kato-Katz thick smears and multiplying this number by a factor of six. The ERR will be calculated as:

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

In the primary model we estimate the difference among CRs by using unadjusted logistic regressions. In a subsequent analysis an adjusted logistic regression (adjustment for age, sex, community, weight and height) will be performed.

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

Results from the stool RDT for fecal occult blood will be categorized as negative, trace and positive. For calprotectin, individuals with levels exceeding 50 µg/g will be considered as positive and concentrations be classified into low (51–149 µg/g), medium (150–299 µg/g) and high (≥300 µg/g) intensity [19].

Anthropometric measurements such as height, weight will be translated into weight- and height-related z-scores using readily available Stata macros calculating growth indicators for children 5-19 years [33]. Body mass index and indicators for muscle and fat tissue such as MUAC and triceps skinfold thickness will serve as indicators for all ages and further be classified using a percentiles approach to compare within populations [34].

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 [23].

Morbidity indicators with continuous values (e.g. anthropometric, Hb, mean physical functioning scores) will be compared in a first step within and between groups using independent and paired t-test statistics while chi-square testing will be performed for binary/categorical outcomes (e.g. anemia, malnutrition categories, fecal calprotectin intensity, blood in stool). To compare individual's changes in malnutrition categories as an effect from treatment McNemar's test will be applied. In a second step, adjusted repeated measures linear and logistic regressions using generalized estimating equation (GEE) models will be performed to assess development of morbidity indicators and related factors be investigated.

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

7.4 Description of data management

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

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 pseudonymised data and will only be accessible to the local principal investigator. All data that have been hand-entered in the database will be verified by a double-key entry procedure in a validated electronic data base system and error, range and consistency checks will be programmed. Any discrepancies will be reviewed against the hard copy CRF and corrected. Electronic data files will be stored on secured network drives with restricted access for study personnel only. Data analysis will be conducted with pseudonymised data and reporting of findings will be fully anonymised.

Essential infrastructure such as lockable cabinets for safe storage of hardcopy data will be made available. Network drives with restricted access for authorized personnel only and appropriate analysis software are available.

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

All protocol modifications must be documented in writing. A protocol amendment can be initiated by either the Sponsor/PI or any Investigator. The Investigator will provide the reasons for the proposed amendment in writing and will discuss with the Sponsor/PI and Co-PIs. Any protocol amendment must be approved and signed by the Sponsor/PI and must be submitted to the appropriate Independent Ethics Committee (IEC) for information and approval, in accordance with local requirements, and to regulatory agencies if required. Approval by IEC must be received before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial 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) and patient liability insurances will be issued in Pemba (Tanzania).

8.3 Project management

The trial team will include the PI (Prof. Jennifer Keiser), three Co-PIs (Dr. Eveline Hürlimann, Mr. Shaali Ame and Mr. Said Ali), a PhD student, a trial statistician (Dr. Jan Hattendorf), as well as two local physicians and laboratory technicians. Prof. Jennifer Keiser, Dr. Eveline Hürlimann, Mr. Shaali Ame and a PhD student will be responsible for staff management, communication with the collaborative group, recruitment monitoring, data management, safety reporting, analysis, report writing and dissemination of the trial results. Mr. Shaali Ame 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 schools. Dr. Eveline Hürlimann is responsible for oversight of the study in the three continents.

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 (EKNZ) and Zanzibar (ZAMREC). The study will be undertaken in accordance with the Declaration of Helsinki and good clinical practice (GCP).

9.2 Evaluation of the risk-benefit ratio

Ivermectin in combination with albendazole are well-known, widely used drugs in mass treatment programs against filariasis, and have little and mainly mild AEs (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 *T. trichiura* will be treated with ivermectin (200 µg/kg)-albendazole (400 mg) considering higher efficacy compared to the existing standard treatment (albendazole alone) and recent inclusion as recommended treatment scheme on the Essentials Medicines List [35].

9.3 Subject information and consent

All parents or caregivers of eligible children and all adult participants ≥18 years) will 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. Parents or caregivers and adult participants will have sufficient time for reflection of their child's or their own participation, respectively.

Community meetings will be conducted to explain to caregivers and potential participants the purpose and procedures of the study. Parents or caregivers attending this meeting will receive a small provision to cover their costs for transportation (~US$ 2). One of the parents/caregiver of an eligible individual will be asked to sign a written informed consent form (translated into the local language, *i.e.* Kiswahili) after having had sufficient time for reflection of their child's participation. Children (aged 6-17 years) will be briefed verbally and asked orally for assent. Even if the participant gives oral assent, the parent/caregiver has to sign the consent. Participation is voluntary and individuals have the right to withdraw from the study at any given point in time with no further obligations. Participation itself will not be awarded with compensation.

9.4 Subject confidentiality

The obtained data will be handled strictly confidentially. Only members of the study team will have access to the data. Personal data will be coded for data analysis. The codes will be filled with the participant's identity on a separate file (subject identification list) and stored in a secured place at the local institutions (*i.e.*, Côte d'Ivoire: UFR Biosciences - Université Félix Hophouët-Boigny, Lao PDR: National Institute of Public Health, and Pemba: Public Health Laboratory Ivo de Carneri) and will only be accessible to investigators. 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.

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 include school-aged children, since *T. trichiura* infection occurs often in children; hence this age group is at high risk of infection and is therefore the major target group in MDA campaigns. Our trial will produce more evidence to support the search for a safe and effective treatment of STH infections in children and whole communities.

9.6 Other aspects

Patients are in general treated only in yearly intervals to reduce morbidity from chronic infections. A treatment delay of 3-4 weeks is not expected to cause any problem.

10. Quality control and quality assurance

10.1 Monitoring and auditing

We will work with locally based monitors. These will conduct site visits to the investigational facilities for the purpose of monitoring the study. Details will be described in a separate monitoring plan. The investigator will permit them access to study documentation and the clinical supplies dispensing and storage area. Monitoring observations and findings will be documented and communicated to appropriate study personnel and management. A corrective and preventative action plan will be requested and documented in response to any audit observations. No sponsor initiated audits are foreseen, but audits and inspections may be conducted by the local regulatory authorities or ethics committees. The Investigator agrees to allow inspectors from regulatory agencies to review records and is encouraged to assist the inspectors in their duties, if requested.

10.2 Access to data, handling of data and samples (data protection), archiving (place, duration) and destruction

Information about study subjects will be kept confidential and managed accordingly. 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.

All data on parasitology and questionnaires about AEs and self-reported clinical signs and symptoms will be doubled entered into a database by two independent persons and cross-checked. Discrepancies between data entries will be corrected by consulting the hard copy.

The collected data together with the hard copy CRFs, ICFs and other study documents will be stored at server of the Public Health Laboratory in Pemba and are encrypted with Secure Sockets Layer

The results of the research study will be published, but subjects' names or identities will not be revealed. Records will remain confidential. To maintain confidentiality, the Sponsor-Investigator will keep records in locked cabinets and the results of tests will be coded to prevent association with participant's names. Data entered into the ACCESS data entry mask will be accessible only by authorized personnel directly involved with the study and will be encoded. Subject-specific information may be provided to other appropriate medical personnel only with the subject's permission.

After the study has been completed all samples will be destroyed and research data and related material will be kept 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.

10.3 Data entered directly in the CRF – definition of source data

Source Data are the clinical findings and observations, laboratory data maintained at the study site. Source data are contained in **source documents**. Local authorities are allowed to access the source data. Data will be entered directly onto the CRFs. The CRF is considered as a source document. All CRFs will be kept for at least 15 years.

The study site 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.

10.4 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. This study is anticipated to be no greater than minimal risk to participants.

10.5 Study Documents: Translations - Reference language

- 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.

11. Dissemination of results and publication

The final results of this study will be published in a scientific journal and presented at scientific conferences. The Bill & Melinda Gates Foundation will be acknowledged as study funder. All results from this investigation are

considered confidential and shall not be made available to any third party by any member of the investigating team before publication. A summary of study conclusions will be shared with ZAMREC.

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13. Appendix

13.1 Household-based questionnaire

"Questionnaire_ALB-IVM-COADMIN_V1.01_19.01.18" referring to "Protocol_ ALB-IVM-COADMIN _V1.01_19.01.18"

Swiss TPH

Date: |__|__|/|__|__|/2018 Place: _____ Interviewer: _____	**Household ID:** |__|__|__|__|
Participant ID: |__|__|__|__| Sex: |__| [M/F] Age: |__|__|	

A) Socioeconomic factors

A1. Which of the following items do you have in your household/do you own?

Note: only owned by the respective household NOT other family members living in other households. MULTIPLE CHOICES

Item		Item	
1. Books/newspapers	☐ Yes ☐ No	9. Car	☐ Yes ☐ No
2. Radio	☐ Yes ☐ No	10. Electricity (cable)	☐ Yes ☐ No
3. Television	☐ Yes ☐ No	11. Charcoal for cooking	☐ Yes ☐ No
4. Video/DVD player	☐ Yes ☐ No	12. Gas for cooking	☐ Yes ☐ No
5. Fan	☐ Yes ☐ No	13. Cell phone	☐ Yes ☐ No
6. Refrigerator/Freezer	☐ Yes ☐ No	14. TV signal: Cable	☐ Yes ☐ No
7. Bike	☐ Yes ☐ No	15. TV signal: Box receiver	☐ Yes ☐ No
8. Motorbike	☐ Yes ☐ No	16. TV signal: Satellite dish	☐ Yes ☐ No

A2. What are the walls of your house(s) made of?

Note: If they have several houses give priority to the best equipped building. MULTIPLE CHOICES

1. Bamboo/palm leaves	☐ Yes ☐ No	4. Clay & stones/concrete mix	☐ Yes ☐ No
2. Wood (planks or boards)	☐ Yes ☐ No	5. Concrete/Bricks/Geo-concrete	☐ Yes ☐ No
3. Wooden frame & clay only	☐ Yes ☐ No	6. Other: _____	☐ Yes ☐ No

A3. What is the floor of your house(s) made of?

Note: If they have several houses give priority to the best equipped building. MULTIPLE CHOICES

1. Soil	☐ Yes ☐ No	5. Concrete/Geo-concrete	☐ Yes ☐ No
2. Clay	☐ Yes ☐ No	6. Tiles/tiles-concrete mix floor	☐ Yes ☐ No
3. Bamboo/palm leaves	☐ Yes ☐ No	7. Other: _____	☐ Yes ☐ No
4. Wood (planks or boards)	☐ Yes ☐ No		

A4. What is the roof of your house(s) made of?

Note: If they have several houses give priority to the best equipped building. MULTIPLE CHOICES

1. Bamboo/palm leaves/grass	☐ Yes ☐ No	4. Corrugated metal (aluminum, zinc)	☐ Yes ☐ No
2. Wood (planks or boards)	☐ Yes ☐ No	5. Tiles	☐ Yes ☐ No
3. Plastic	☐ Yes ☐ No	6. Other: _____	☐ Yes ☐ No

B) Presence of sanitation and water structures at household level

B1. Do you dispose of any shower at your household? And what material is its floor made of?

Note: Verify that it is their private shower and not a common/shared shower belonging to somebody else. SINGLE CHOICE

☐ 1. No shower
☐ 2. Shower with sand/earth floor
☐ 3. Shower with gravel floor
☐ 4. Shower with tiles/tiles-concrete mix floor
☐ 5. Shower with concrete floor
☐ 6. Other: _____
☐ 7. Common/shared shower

B2. Do you dispose of any latrine/toilet at your household?

Note: Verify that it is their private latrine/shower and not a common/shared latrine/toilet belonging to somebody else. SINGLE CHOICE

☐ Yes, a private latrine
☐ Yes, a shared/common latrine → *jump to B5*
☐ No → *jump to B5*

B3. What material is the latrine's/toilet's floor/slab made of?

SINGLE CHOICE

☐ 1. Wood/Bamboo & clay
☐ 2. Wood (solid)
☐ 3. Concrete
☐ 4. Ceramic tiles (& concrete)
☐ 5. Other: _____

B4. Does the latrine/toilet dispose the following facilities/assets?

Note: For better explanation/If assets unclear show pictures. MULTIPLE CHOICES

Facility/asset		**Facility/asset**	
1. Lid to close the hole	☐ Yes ☐ No	8. Ventilating tube	☐ Yes ☐ No
2. Hand washing facility *(e.g. jar)*	☐ Yes ☐ No	9. Unlined pit	☐ Yes ☐ No
3. Walls of woven plants / plastic / wooden frame&clay	☐ Yes ☐ No	10. Bamboo/Wood-lined pit	☐ Yes ☐ No
4. Walls of wood (solid)	☐ Yes ☐ No	11. Concrete/Brick-lined pit	☐ Yes ☐ No
5. Walls of bricks/concrete	☐ Yes ☐ No	12. Flush/pour-flush into pit latrine	☐ Yes ☐ No
6. Metal roof	☐ Yes ☐ No	13. Connection to septic tank	☐ Yes ☐ No
7. Door (solid)	☐ Yes ☐ No	14. Connection to piped sewer system	☐ Yes ☐ No

B5. Where do you get your water for drinking/washing from?

Note: If they mention storage facilities of water (e.g. barrel, tank) ask them what kind of water is in them and then record the answer. Drink=used as drinking water, Wash=used to wash, No=not used

Water type	Drink	Wash	No	**Occasion**	Drink	Wash	No
1. River/Lake/Pond/Dam				5. Tap			
2. Open well/borehole				6. Rain water			
3. Closed well/borehole				7. Other			
4. Public pump				(specifiy):			

B6. Do you have any water facilities that belong to your household/compound?

MULTIPLE CHOICES

1. None	☐ Yes ☐ No	4. Private closed borehole/well	☐ Yes ☐ No
2. Water storage recipients	☐ Yes ☐ No	5. Private tap	☐ Yes ☐ No
3. Private open borehole/well	☐ Yes ☐ No	6. Other: _____	☐ Yes ☐ No

C) Hygiene attitudes and practices

C1. Is open defecation practiced in your community/village?

☐ Yes ☐ No → *jump to C3*

C2. Where do people/children defecate openly?

MULTIPLE CHOICES

1. Bushes very close to houses	☐ Yes ☐ No	5. Close to water bodies *(river, pond)*	☐ Yes ☐ No
2. Surroundings of the school	☐ Yes ☐ No	6. Around but outside the village	☐ Yes ☐ No
3. On the way to the plantation	☐ Yes ☐ No	7. Close to/On waste dumping site	☐ Yes ☐ No
4. In the field/plantation	☐ Yes ☐ No	8. Other: _____	☐ Yes ☐ No

C3. Do you show and explain to the children of your household that hand washing is important?

☐ Yes ☐ No → *jump to C5*

C4. When you speak about hand washing, WHEN/IN WHICH OCCASIONS do you tell them they have to wash them?

Note: SP=spontaneously mentioned, PR=mentioned after probing, No=Not mentioned

Occasion	SP	PR	No	**Occasion**	SP	PR	No
1. Before eating				7. After defecation			
2. After eating				8. After washing laundry			
3. Before cooking				9. Whenever they are dirty			
4. Before feeding the baby				10. Before praying			
5. After cleaning the baby				11. Other			
6. Before getting dressed				(specifiy):			

C5. The water you use to drink/wash: how do you use it?

MULTIPLE CHOICES

1. Use directly	☐ Yes ☐ No	5. Put in bottle & expose to sunlight	☐ Yes ☐ No
2. Boil it	☐ Yes ☐ No	6. Filter it	☐ Yes ☐ No
3. Add tablets before drinking	☐ Yes ☐ No	7. Other: _____	☐ Yes ☐ No
4. Add bleach/soap before washing things/myself	☐ Yes ☐ No		

5. Trial protocol Cote d'Ivoire:

Efficacy and safety of ivermectin and albendazole co-administration in school-aged children and adults infected with *Trichuris trichiura*: a multi-country randomized controlled trial

Protocol Number	1		
Version Number	1.01	**Document Date**	12.06.2018
Sponsor Contact	Prof. Dr. Jennifer Keiser, Swiss Tropical and Public Health Institute, Tel.: +41 61 284-8218 Fax: +41 61 284-8105 E-mail: jennifer.keiser@unibas.ch		
Principle Investigator	Prof. Dr. Jennifer Keiser, Swiss Tropical and Public Health Institute, Tel.: +41 61 284-8218 Fax: +41 61 284-8105 E-mail: jennifer.keiser@unibas.ch		
Funding Agency	Bill and Melinda Gates Foundation		

1. General information

I. List of investigators and other persons involved

Title	Names	Institution	Position	Function in trial
Prof. Dr.	Jennifer Keiser	Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland	Unit head	Principal Investigator
Dr.	Eveline Hürlimann	Swiss TPH	Postdoc	Co-PI
Dr.	Jessica Schulz	Swiss TPH	Postdoc	Co-PI
Dr.	Jean Coulibaly	Swiss TPH / Université Félix Hophouët-Boigny (UFHB), Abidjan, Côte d'Ivoire	Group leader	Co-PI
Dr.	Yves N'Gbesso	Departement d'Agboville, Centre de Santé Urbain d'Azaguié, Azaguié	Medical doctor	Study physician
Dr.	Jan Hattendorf	Swiss TPH	Project leader	Statistician

II. Signatures

Statistician

Signature		Date of Signature 12.06.2018
Name	Jan Hattendorf	
Title	Dr.	
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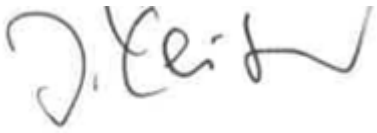
Principal investigator

Signature		Date of Signature 12.06.2018
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Phone	+41 61 284-8218	

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-Principal investigator

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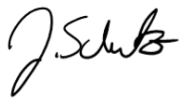
Signature		Date of Signature 12.06.2018
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Table of contents

III. Abbreviations

AE	Adverse event
AUC	Area under the curve
CI	Confidence interval
CNER	Comité Nationale d'Ethique de la Recherche
CR	Cure rate
CRF	Case report form
CSRS	Centre Suisse de Recherches Scientifiques en Côte d'Ivoire
DF	Dose-finding
DPML	Direction de la Pharmacie, du Médicament et des Laboratoires
EKNZ	Ethikkomission Nordwest- und Zentralschweiz
EML	Essential medicine list
EPG	Eggs per gram
ERR	Egg reduction rate
GCP	Good clinical practice
GEE	Generalized estimating equation
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
MDA	Mass drug administration
MIC	Minimal inhibitory concentration
MUAC	Mid-upper arm circumference
PC	Preventive chemotherapy
PCR	Polymerase chain reaction
PI	Principal investigator
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/pharmacodynamic
RDT	Rapid diagnostic test
SAE	Serious adverse event
SOP	Standard operating procedure
STH	Soil-transmitted helminth
Swiss TPH	Swiss Tropical and Public Health Institute
SUSAR	Suspected unexpected serious adverse reaction
WHO	World Health Organization

IV. Synopsis

Sponsor/Sponsor-Investigator	Prof. Dr. Jennifer Keiser
Study Title	Efficacy and safety of ivermectin and albendazole co-administration in school-aged children and adults infected with *Trichuris trichiura*: a multi-country randomized controlled trial
Short title	Efficacy and safety of IVM/ALB co-administration
Protocol Number, Date and Version	1, 12.06.2018, v1.01
Trial registration	Has been registered on ClinicalTrials.gov (reference: NCT 03527732)
Clinical phase	Phase 3 trial
Sample size	1960 (600 participants in each of 3 settings for the parallel group trial including 160 participants for the dose-finding (DF) study)
Indication	*Trichuris trichiura* infection (eggs in stool)
Investigational Product and Reference Treatment	Ivermectin and albendazole
Study Rationale	To provide evidence on a) potentially enhanced efficacy by combining the standard drug albendazole with ivermectin in school-aged children and adults against infection with *T. trichiura*. b) effective doses of ivermectin in combination with albendazole in school-aged children against infection with *T. trichiura*.
Study Objectives	To compare the efficacy and safety of: (a) standard doses of co-administered ivermectin (200 µg/kg) and albendazole (400 mg) compared to albendazole (400 mg) monotherapy in community members aged 6-60 years and (b) ascending doses of ivermectin ((i) 200 µg/kg, (ii) 400 µg/kg, and (iii) 600 µg/kg) co-administered with albendazole (400 mg) in school-aged children (6-12 years) infected with *T. trichiura* and to measure ivermectin and albendazole disposition in children using a microsampling device.

	Our **primary objective** is to comparatively assess the efficacy in terms of cure rates (CRs) against *T. trichiura* infections among school-aged children and adults of the following oral treatment regimens: a) in a parallel group trial: Albendazole (400 mg)/ivermectin (200 µg/kg) combination Albendazole (400 mg) monotherapy b) in the DF study (school-aged children only): Albendazole (400 mg)/ivermectin (200 µg/kg) combination Albendazole (400 mg)/ivermectin (400 µg/kg) combination Albendazole (400 mg)/ivermectin (600 µg/kg) combination Placebo The **secondary objectives** of the trial are: a) To evaluate the safety and tolerability of the treatment regimens b) To compare the egg reduction rate (ERR) of the treatment regimens (combination *vs*. monotherapy and ascending doses of the combination) against *T. trichiura* c) To determine the CRs and ERRs of the drugs in study participants (6-60 years) infected with hookworm, *Ascaris lumbricoides* and *Strongyloides stercoralis* d) To investigate potential extended effects on follow-up helminth prevalences (6 and 12 months post-treatment) of the two standard-dose treatment regimens (as assessed among participants with cleared infection on days 21 and 180) e) To compare CRs based on infection status determined by novel polymerase chain reaction (PCR)-based and standard microscopic diagnosis f) To assess potential differences in susceptibility to the treatment regimen between the hookworm species, *Necator americanus*, *Ancylostoma duodenale* and *A. ceylanicum*, as classified through the novel PCR-based diagnosis g) To characterize *T. trichiura* strains from different epidemiological settings and investigate potential resistance markers using a deep sequencing analysis

	h) To determine optimal timing for measuring anthelmintic efficacy in *T. trichiura* infection i) To evaluate potential benefits from deworming on morbidity indicators and nutritional parameters j) To determine an exposure (including length of time that the drug concentration is above the minimal inhibitory concentration (MIC), Cmax, area under the curve (AUC))-response correlation of ivermectin and albendazole in school-aged children
Study design	Double blind, randomized controlled trial
Study product / intervention	Administration of a single oral dose of ivermectin + albendazole
Comparator(s)	main trial: albendazole (400 mg) monotherapy, DF study: placebo
Key inclusion / Exclusion criteria	**Inclusion:** School-aged children and adults (6-60 years) infected with *T. trichiura* with at least two slides of the quadruple Kato-Katz thick smears positive and infection intensities of at least 100 eggs per gram of stool (EPG), agreeing to comply with study procedures, including provision of two stool samples at the beginning (baseline) and on three follow-up assessments (approximately 3 weeks, 6 months, and 12 months later), written informed consent signed by parents and/or caregivers for children/adolescents; and written assent by child/adolescent (aged 6-20 years). **Exclusion:** No written informed consent by individual/parents and/or caregiver, any clinically relevant abnormality (including severe anemia or clinical malaria) or history of acute or severe chronic disease (*e.g.* cancer, diabetes, chronic heart, liver or renal disease), recent use of anthelminthic drug (past 4 weeks), attending other clinical trials during study, negative diagnostic or low egg count (less than 100 EPG or less than 2 out of 4 slides positive) result for *T. trichiura*, known allergy to study medication, pregnancy or lactating in the 1st week after birth, taking medication with known interaction on study drugs.
Primary Endpoints	*T. trichiura* infection status assessed by Kato-Katz 14-21 days after treatment
Secondary Endpoints	• ERR against *T. trichiura* • CRs and ERRs against *A. lumbricoides*, hookworm and *S. stercoralis* • Adverse events • Infection status assessed by PCR • Pharmacokinetic parameters for ivermectin and albendazole in school-aged children

Exploratory Endpoints	• Molecular characterization and resistance markers of *T. trichiura* • Optimal timing for drug efficacy assessment in *T. trichiura* infection • Nutritional status • Morbidity indicators
Interim Analyses	None
Study Duration	14 months
Schedule	06/2018 of first-participant in (planned) 08/2019 of last-participant out (planned)
Study centers	Multinational study with trial sites in Côte d'Ivoire, Lao PDR and Pemba Island (Tanzania)
Measurements & procedures	Two stool samples (each of a minimum of 15 grams) will be collected if possible on two consecutive days or otherwise within a maximum of 5 days. The medical history of the participants will be assessed with a standardized questionnaire, in addition to a clinical examination carried out by the study physician before treatment. All participants will be interviewed before treatment, 3 and 24 hours and 3 weeks after treatment about the occurrence of adverse events. Children aged 6-16 years will additionally be asked to rate their own physical functioning by replying to a pre-tested questionnaire at baseline and 6 and 12 months after treatment. The efficacy of the treatment and potential extended effects on follow-up prevalence will be determined 14-21 days, 6 months and 12 months post-treatment by collecting another two stool samples. Subjective treatment satisfaction will be assessed 3 hours, 3 weeks and 6 months after treatment to investigate relationship with treatment compliance and observed efficacy in reducing egg output and morbidity. All stool samples will be examined with duplicated Kato-Katz thick smears for *T. trichiura*, *A. lumbricoides* and hookworm. *S. stercoralis* infections will be identified using the Baermann technique and recorded qualitatively as larvae-positive or negative. For subsequent PCR-analysis a portion of 1.5-2 g of stool from each specimen will be preserved in 70% ethanol and shipped to a reference laboratory at Swiss TPH in Switzerland. At baseline and in the first follow-up (3 weeks post treatment) an additional portion of stool (1.5-2 g) from a subsample of 10 participants identified with heavy intensity infections in each case and study setting will be preserved in 95% ethanol, shipped to the same reference laboratory and subjected to deep sequencing for characterization of *T. trichiura* strains and investigation of potential resistance markers. Fecal occult blood and calprotectin in stool as markers for gut morbidity and inflammation will be detected using a rapid diagnostic test and an immunoassay, respectively. A subsample of 30 participants will be asked to provide a daily stool sample for a period of up to 4 weeks to monitor dynamics

	of *T. trichiura* egg output for subsequent determination of the optimal timing for drug efficacy assessment. Individuals found *T. trichiura* positive 6 months after baseline will receive a second round of treatment according to their group scheme. Each participant will be asked to provide a finger-prick blood sample for hemoglobin measurement, a rapid diagnostic test (RDT) for *Plasmodium* spp. and where applicable a biplex RDT for lymphatic filariasis/onchocerciasis at baseline and 6 and 12 months after treatment. At the same time points anthropometric measurements (*i.e.* height, weight, mid-upper arm circumference (MUAC) and skinfold thickness) will be taken for all participants. In addition, a venous blood sample (~8 ml) will be taken from each participant to assess biochemical blood parameters as proxies for vital organ functioning (*e.g.* complete blood count, urea, creatinine, transaminases etc.) and nutritional indicators for micro- (*i.e.* (pro-) vitamins, inflammation markers, and iron/ferritin) and macronutrient (*i.e.* albumin) deficiencies at baseline, day 21, day 180 and day 360. To all participating households, a questionnaire will be administered assessing information on socioeconomic characteristics and access to sanitation, water facilities, and hygiene behavior. For the assessment of pharmacokinetic parameters within the DF study the participating school-aged children (6-12 years) will be sampled using finger pricking for microsampling at 0, 1, 2, 3, 4, 5, 6, 7, 9, 24, 48 hours post-dosing.
Statistical Analyses	An available case analysis 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 egg-positive subjects at baseline who become egg-negative after treatment. Differences among CRs (between treatment arms and between diagnostic approaches) will be analysed by using crude and adjusted logistic regression modeling (adjustment for age, sex and weight). Geometric and arithmetic mean egg counts will be calculated for the different treatment arms before and after treatment to assess the corresponding ERRs. Bootstrap resampling method with 5,000 replicates will be used to calculate 95% confidence intervals (CIs) for differences in ERRs. Further secondary outcomes – as nutritional and morbidity indicators - will be analysed using logistic and linear regression as appropriate. To compare individual's changes in nutrition/morbidity categories as an effect from treatment McNemar's test will be applied. The analysis after 6 and 12 month of follow-up will be complemented by generalized estimating equation (GEE) models with independent correlation structure and empirical estimators to account for missing data. Nonlinear mixed-effects modeling will be used to determine pharmacokinetic parameters.

GCP statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ICH-GCP E6 (R2) as well as all national legal and regulatory requirements.
Key explanation for the inclusion of children	This study will involve school-aged children, since an infection with *T. trichiura* occurs most often in children and they are further the main target group of deworming campaigns.
Recruitment procedure	The parallel group trial will be conducted as a multi-country study with two settings in Africa and one in Asia recruiting each 600 community members: • West African setting: Côte d'Ivoire • East African setting: Pemba (Zanzibar, Tanzania) • Asian setting: Lao PDR The DF study will be embedded in the trial and implies the recruitment of an additional 160 school-aged children (6-12 years) to be able to include 40 children per arm in Côte d'Ivoire. The studies will be conducted in areas with moderate to high *T. trichiura* endemicity (communities with a prevalence ≥ 25%) identified from earlier studies and/or based of experience of the local collaborating teams. They will be implemented as community-based studies in order to recruit participants from a broad age range (6-60 years). Ideally, entire communities with a population size of < 1000 inhabitants will be included in the study for pre-screening and identification of *T. trichiura* cases to avoid potential selection bias of households. To identify all potentially eligible households of the respective communities and its composition in terms of age groups a preceding population census will be conducted.
Coverage of damages	Winterthur Police Nr. 4746321, BERACA Côte d'Ivoire, No: to be issued
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.

2. Background information

Albendazole and mebendazole are the most widely used drugs for preventive chemotherapy (PC) campaigns against soil-transmitted helminth (STH) infections. Albendazole is characterized by high cure rates (CRs) and egg reduction rates (ERRs) against infections with *Ascaris lumbricoides* (95.7% and 98.5%) and hookworm infections (79.5 and 89.6%). Lower efficacy is observed against *Trichuris trichiura* infections (CR 30.7%, and ERR of 49.9%) [1].

Therapies combining two or more drugs are widely advocated in different therapeutic areas such as tuberculosis, malaria, HIV/AIDS or cancer. The underlying rationale for multifactorial pharmacological treatment varies with the disease and includes the protection against the selection of drug-resistance, and hence, a prolongation of the life-span of effective and available drugs, and to increase and broaden the efficacy over drugs being administered in mono-therapy [2].

A recent review and meta-analysis found that ivermectin co-administered with albendazole is highly efficacious for the treatment of *T. trichiura* and is comparatively more efficacious than albendazole alone (Figure 1) [3]. Efficacy of ivermectin and albendazole against *A. lumbricoides* and hookworm are comparable and in some cases more efficacious than albendazole alone. Summarized efficacy measures of albendazole, mebendazole, and ivermectin against trichuriasis from a recent review [1] and earlier trials [4, 5] are shown in Table 1.

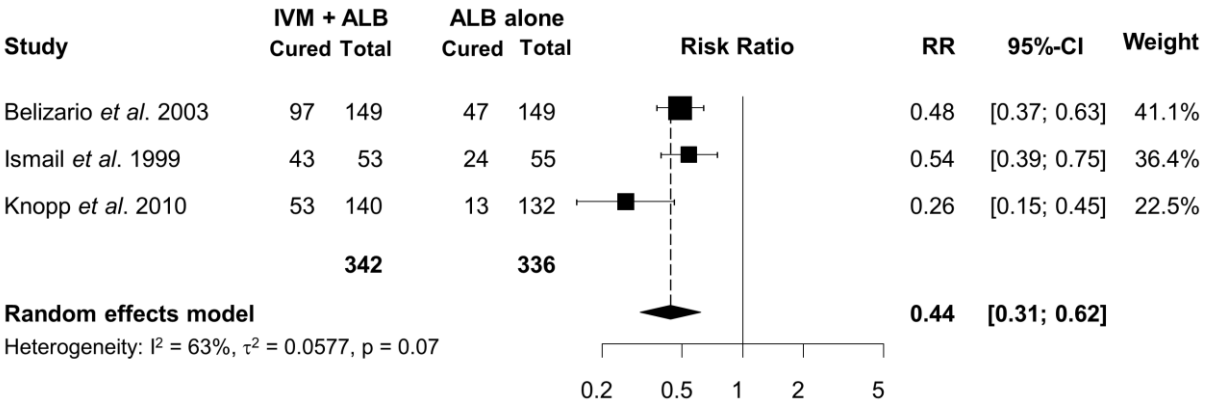

Figure 1. Forest plot displaying the results of a random-effects meta-analysis of the effect of the co-administration of albendazole-ivermectin on the number of patients infected with *T. trichiura* compared to albendazole alone.

Table 1. Average CRs and ERRs of albendazole and mebendazole for *T. trichiura* from a recent review [1] as well as findings from studies investigating ivermectin [4, 5]

Drug	CR (%)	95% CI	ERR (%)	95% CI
Albendazole	30.7	(21.0, 42.5)	49.9	(39.0, 60.6)
Mebendazole	42.1	(25.9, 60.2)	66.0	(54.6, 77.3)
Ivermectin	11-35	NA	43-98	NA

NA, not applicable

The individual studies included in the review are summarized in Table 2. All four studies are randomized controlled trials and used the standard dose of 200 µg/kg ivermectin and 400 mg albendazole [4, 6-8]. Against infections with *T. trichiura*, CRs ranging from 27.5-81.1%, ERR based on geometric mean ranging from 91.3-99.7%, and ERR based on arithmetic mean ranging from 85.6-97.5% were observed. CRs for *T. trichiura* observed in Asian settings were higher than in African settings. One reason for this finding may be differences in the study design and quality (*e.g.* in terms of diagnostic approach used). Another possible reason recently highlighted is genetic diversity of *T. trichiura* strains and variation in susceptibility to anthelmintics and/or drug resistance [9-11]. Interestingly, the higher efficacy of ivermectin in combination with albendazole translated – at least in some settings – into lower prevalences even after one year [4, 12]. The efficacy of albendazole-ivermectin against *A. lumbricoides* was excellent (CRs >78% and ERRs >99.5%), while moderate CRs (50-66.7%) and high ERRs (>95.4%) were observed against hookworm.

Table 2. Known efficacy of co-administered ALB-IVM[a] against *T. trichiura*:

Study	**Setting**	**Cure rate in % (n_{neg}/n)**	**Eggs per gram (pre/post)**	**Egg reduction rate in %**
Ismail et al. 1999	Sri Lanka	81.1% (43/53)	1544.0/78.7 (unkwn)	94.9% (unkwn)
Belizario et al. 2003	Philippines	65.1% (97/149)	4948.1/122.5 (ar) 550.0/1.9 (geo)	97.5% (ar) 99.7% (geo)
Knopp et al. 2010	Tanzania (Pemba)	37.9% (53/140)	127/11 (geo)	91.3% (geo)
Speich et al. 2015	Tanzania (Pemba)	27.5% (30/109)	1059/153 (ar) 489/27 (geo)	85.6% (ar) 94.5% (geo)
All studies		**49.4% (223/451)**		

[a]*Considered doses: albendazole=400 mg, ivermectin=200 µg/kg*

ar=arithmetic mean, geo=geometric mean, unkwn=unknown mean

The WHO Expert Committee met from March 27-31, 2017 and, based on review of a dossier suggesting inclusion of ivermectin as an anthelmintic in the Essential Medicines List, made the following recommendation:

"…adding ivermectin on the Essential Medicines List under the section intestinal anthelminthic for use against Strongyloides stercoralis and STH. It may be used in combination with albendazole for treatment of soil-transmitted helminthiasis."

This important milestone paves the way for further, standardized trials to evaluate the efficacy of this combination among school-aged children in a range of epidemiological settings. In addition, the combination should be evaluated among adults, as there is growing interest in broadening deworming to include adults in order to move from morbidity control toward interruption of transmission [13, 14].

In the proposed work, three trials are planned across a range of transmission settings, including Côte d'Ivoire, Lao PDR, and Pemba (Tanzania). Follow-up will be conducted at 1, 6, and 12 months to inform treatment frequency. Results from these trials will inform decisions on how the combination could be introduced into

existing mass drug administration (MDA) programs and therefore provide a valuable adjunct tool for interrupting STH transmission.

3. Trial objective and purpose

The overall goal of the study is to assess the efficacy and safety of co-administered albendazole and ivermectin versus albendazole monotherapy (standard of care) against *T. trichiura* infections in children and adults (6-60 years) in different transmission settings and geographies. Embedded in this trial a smaller dose-finding (DF) study with the goal to investigate efficacy, safety and pharmacokinetic parameters of ascending doses of ivermectin ((i) 200 µg/kg, (ii) 400 µg/kg, and (iii) 600 µg/kg) co-administered with albendazole (400 mg) in school-aged children infected with *T. trichiura* will take place.

We hypothesize that albendazole-ivermectin has a higher efficacy against *T. trichiura* infections than albendazole alone, and hence, the efficacy against all three STH species (*A. lumbricoides*, *T. trichiura*, and hookworm) and *Strongyloides stercoralis* will be increased.

The **primary objective** of the trial is to comparatively assess the efficacy in terms of CR against *T. trichiura* infections among school-aged children and adults from three different epidemiological settings and monitored over a 12-month period of the following two oral treatment regimens:

- Albendazole/ivermectin combination
- Albendazole monotherapy

A DF study will be implemented in the trial with the objective to understand the dose-dependent efficacy and pharmacokinetic profile of the co-administration of albendazole and ivermectin in school-aged children (6–12 years) with the following four oral treatment regimens:

- Albendazole (400 mg) /ivermectin (200 µg/kg) combination
- Albendazole (400 mg) /ivermectin (400 µg/kg) combination
- Albendazole (400 mg) /ivermectin (600 µg/kg) combination
- Placebo

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

a) To evaluate the safety and tolerability of the treatment regimens
b) To compare the ERRs of the treatment regimens (combination *vs*. monotherapy and ascending doses of the combination) against *T. trichiura*
c) To determine the CRs and ERRs of the drugs in study participants (6-60 years) infected with hookworm, *A. lumbricoides* and *S. stercoralis*
d) To investigate potential extended effects on follow-up helminth prevalences (6 and 12 months post-treatment) of the two standard-dose treatment regimens (as assessed among participants with cleared infection on days 21 and 180)

e) To compare CRs based on infection status determined by novel polymerase chain reaction (PCR)-based and standard microscopic diagnosis
f) To assess potential differences in susceptibility to the treatment regimen between the three hookworm species, *Necator americanus, Ancylostoma duodenale and A. ceylanicum*, as classified through the novel PCR-based diagnosis
g) To characterize *T. trichiura* strains from different epidemiological settings and investigate potential resistance markers using a deep sequencing analysis
h) To determine optimal timing for measuring anthelmintic efficacy in *T. trichiura* infection
i) To evaluate potential benefits from deworming on morbidity (clinically evaluated and self-rated from questionnaire interviews) and nutritional indicators
j) To determine an exposure (including length of time that the drug concentration is above the minimal inhibitory concentration (MIC), Cmax, area under the curve (AUC))-response correlation of ivermectin and albendazole in school-aged children

4. Methodology

4.1 Primary and secondary endpoint

T. trichiura infection status assessed by Kato-Katz 14-21 days after treatment will be the primary endpoint and the main outcome for efficacy be expressed as cure rate (CR) (*i.e.* conversion from being egg positive pre-treatment to egg negative post-treatment) and egg reduction rate (ERR) (secondary end point). Secondary endpoints include further infection status with *A. lumbricoides*, hookworm and *S. stercoralis* and related efficacy measures, adverse events, infection status assessed by PCR and key pharmacokinetic parameters in school-aged children. In addition, optimal timing for drug efficacy assessment in *T. trichiura* infection will be determined, *T. trichiura* strains will be described and potential resistance markers evaluated using deep sequencing and potential benefits on nutritional and morbidity indicators from treatment assessed (exploratory end points).

4.2 Type of trial

Double blind randomized controlled trial.

4.3 Trial design

4.3.1 Baseline survey and screening

Parallel group multi-country study

A randomized-controlled trial will be conducted with two treatment arms to be followed-up over a 12 months period with an intermediate re-treatment of participants found re-infected after 6 months (Figure). This parallel group trial will be conducted as a multi-country study; thus, in each setting a separate trial according to the design described below will be set up, to provide a better basis for the subsequent generalization of its findings. This arises from the possibility of recruiting the subjects from a wider population and of administering the medication in a broader range of clinical settings, thus presenting an experimental situation that is more typical of future use. The study includes one baseline and three follow-up assessments at 3 weeks (day 21), 6 months (day 180), and 12 months (day 360).

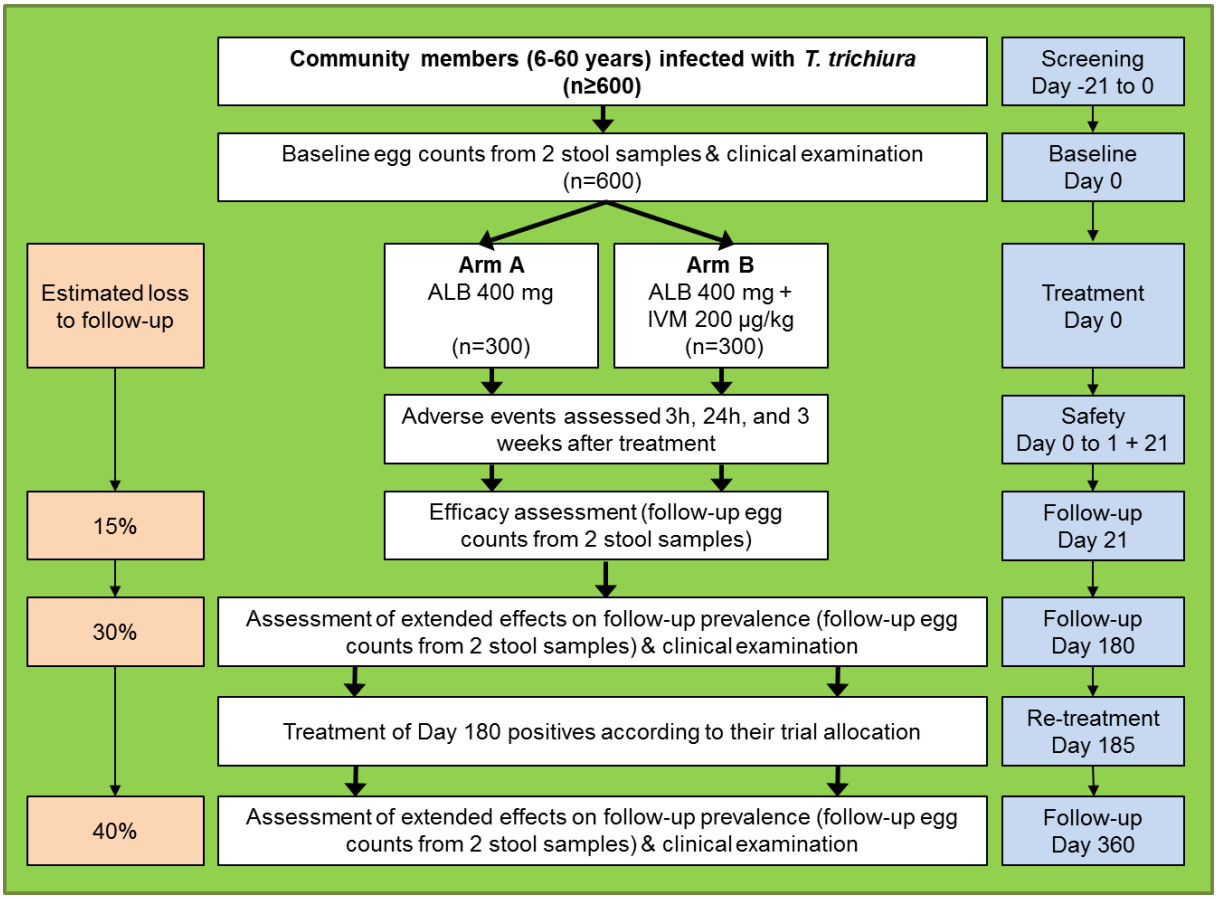

Figure 2. Design and timeline of the randomized-controlled trial to be implemented in each of three settings.

The study is designed as a two-armed trial including one arm with a single drug administration (arm A; albendazole) and one arm with combined treatment through co-administration of separate tablets (arm B; albendazole and ivermectin).

The trial will be conducted as a multi-country study with two settings in Africa and one in Asia, namely Côte d'Ivoire, Pemba (Zanzibar, Tanzania) and Lao PDR.

At baseline, all participants will be asked to provide two stool samples of at least 15 grams each (within a maximum of 5 days). From every stool specimen, duplicate Kato-Katz thick smears (41.7 mg each) [15] will be prepared and read under a microscope for eggs of *T. trichiura*, *A. lumbricoides* and hookworm by experienced technicians. A small amount of feces (~10 mg and 60 µg, respectively) will further be tested on fecal occult blood and calprotectin as proxies for gut morbidity and inflammation using a rapid diagnostic test an immunoassay, respectively [16]. Additionally, a portion of 1.5-2 g of stool from each specimen will be preserved in 70% ethanol and shipped to a reference laboratory at the Swiss Tropical and Public Health Institute (Swiss TPH, Basel, Switzerland) for PCR analysis [17]. While discrimination of hookworm species via morphological comparison during microscopy of Kato-Katz slides is not feasible [18], PCR will allow to accurately determining efficacy and for further classification of hookworm infection into the three species *N. americanus, A. duodenale* and *A. ceylanicum*. The remains of each stool sample (ideally 10 to 20 g) will be processed by the Baermann technique for identification of *S. stercoralis* infections and be recorded qualitatively as larvae-positive or negative. At baseline and in the first follow-up (3 weeks post treatment) an additional portion of the second stool sample (1.5-2 g) from a subsample of 10 participants identified with heavy intensity infections in each case (as assed on the first sample) will be preserved in 95% ethanol, shipped to the same reference laboratory at Swiss TPH in Switzerland and subjected to deep sequencing for characterization of *T. trichiura* strains and

investigation of potential resistance markers [19]. A subsample of 30 participants will be asked to provide a daily stool sample for a period of up to 4 weeks to monitor dynamics of *T. trichiura* egg output for subsequent determination of the optimal timing for drug efficacy assessment as has been done for other STH species earlier [20].

A subsequent independent quality control of sample results (approximately 10%) will be conducted. Results are considered correct if the following tolerance margin is not exceeded: (i) No difference in presence/absence of hookworm, *A. lumbricoides* and *T. trichiura*, (ii) egg counts are +/-10 eggs for counts ≤100 eggs or +/-20% for counts >100 eggs (for each species separately) [21]. 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 count per gram of stool (EPG) will be calculated for each treatment arm. All microscopically analyzed quadruplicate Kato-Katz thick smears will be destroyed within one day (after passing the quality control). The same sampling procedure and diagnostic approach will be applied at days 21, 180 and 360 post-treatment.

Patients with filariasis showed significantly higher numbers of adverse events (AE) for treatment with ivermectin in combination with albendazole in earlier studies [22-24]. A rapid diagnostic test (RDT; *i.e.* SD BIOLINE Oncho/LF IgG_4 biplex test) to detect antigens in the blood will therefore be used to identify potential co-infection with *Wuchereria bancrofti* and *Onchocerca volvulus* at baseline, 6 and 12 months post-treatment (before a potential re-treatment). AEs after treating filariasis were mostly mild [3]; the approach of capturing AEs will thus not change but the result of the RDT be used to explain potential differences in AE reporting between filariasis negative and positive participants.

A clinical examination of the study participants assessing general health, anthropometric parameters including height, weight, mid-upper arm circumference (MUAC) and skinfold thickness (i.e. triceps and subscapular skinfolds) as well as tympanic temperature using an ear thermometer will precede the treatment and will be repeated on two follow-up assessments (days 180 and 360) to evaluate potential benefits from deworming. Each participant will be asked to provide a finger-prick blood sample for a RDT for *Plasmodium* spp. infection and to evaluate hemoglobin (Hb) levels using a HemoCue analyzer (Hemocue Hb 301 system; Angelholm, Sweden) following the same (re-)assessment schedule. To assess potential improvement on nutritional indicators for micro- (*i.e.* (pro-) vitamins, inflammation markers, and iron/ferritin) and macronutrient (*i.e.* albumin) deficiencies and dynamics of biochemical blood parameters as a proxy for functioning of vital organs a venous blood sample (approximately 8 ml) will be taken at baseline, day 21, day 180 and 360. The biochemical parameters to be assessed include urea, creatinine, bilirubin, azotemia, Alanine Amino Transferase (ALAT), Aspartate Amino Transferase (ASAT) as well as blood cell counts (*e.g.* hematocrit, erythrocytes and platelets). To avoid accidental treatment of pregnant girls/women all female participants (≥ 10 years) will be asked to provide a urine sample of at least 10 ml to be subjected to a pregnancy RDT on day 0 and day 180.

All trial participants will further be asked about existing clinical symptoms before drug administration. Additionally, they will be asked to provide subjective short-term (*e.g.* convenience of treatment) and long-term (*e.g.* effectiveness in reducing symptoms) treatment satisfaction embedded in the re-assessment questionnaires. As a measure of patient-rated physical functioning and wellbeing all children (6-16 years) will be administered a questionnaire before, 6 and 12 months after treatment, based and adapted from tools already validated in school-aged children from rural settings in Côte d'Ivoire [25] and pre-tested in a comparable school-aged population not otherwise involved in this trial. To adjust for known influencing factors with regard to reinfection and morbidity [26, 27] in the subsequent analysis and to identify risk factors for residual infections [28] a household-based questionnaire will be administered to one adult member of each participating household, assessing information on socioeconomic characteristics, access to sanitation and water facilities as well as hygiene behavior.

DF study with school-aged children

Embedded in the parallel group trial a randomized-controlled DF study assessing ascending doses of ivermectin co-administered with a single dose of albendazole will be implemented. The study is designed as a four-armed trial including ascending doses of ivermectin co-administered with the standard dose of albendazole (arm 1–3) and one placebo arm serving as a comparator (arm 4) (Figure). 160 school-aged children infected with *T. trichiura* will be randomly assigned to arm 1–4. Baseline and screening procedures are identical to the parallel group study. Children in arm 1-3 will be micro sampled on different time points between treatment day 0 and day 2 (at 0, 1, 2, 3, 4, 5, 6, 7, 9, 24, 48 hours post-dosing) in order to obtain pharmacokinetic data while children in arm 4 will provide finger-prick blood samples at day 0 only for RDT assessments.

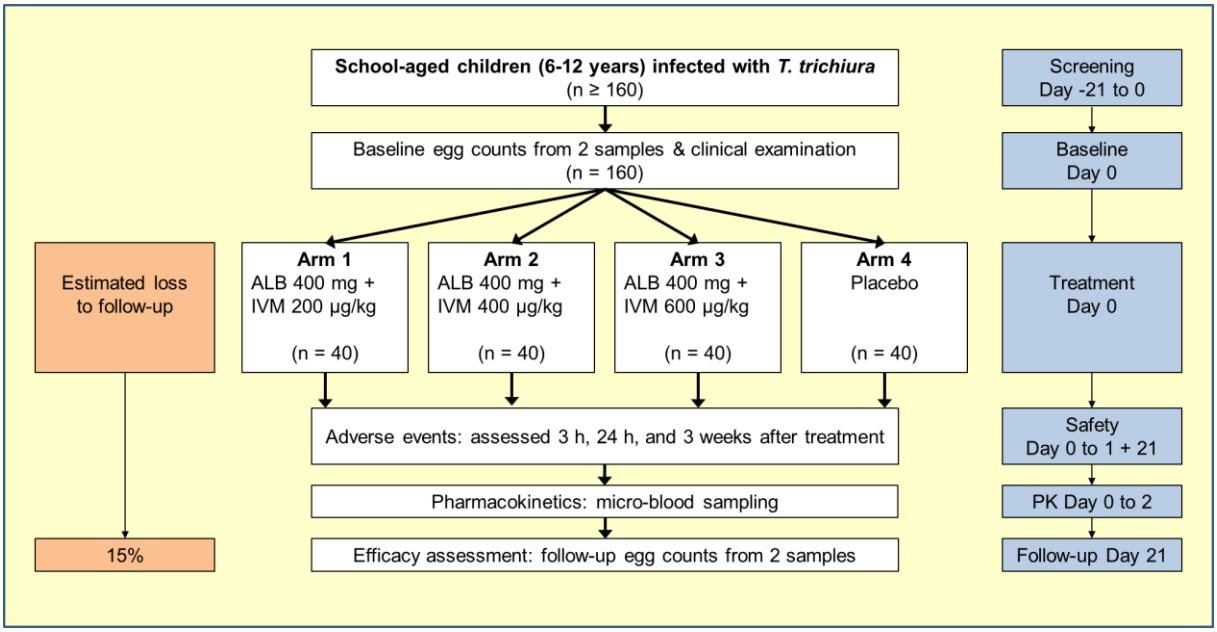

Figure 3. Efficacy, safety and pharmacokinetics of ivermectin-albendazole co-administration: dose-finding study flow.

4.3.2 Assessment of efficacy and other benefits after treatment

Parallel group multi-country and DF study

The efficacy of the treatment will be determined 21 days post-treatment by collecting another two stool samples which will be microscopically examined for *T. trichiura* using duplicate Kato-Katz thick smears and potential co-infection with *S. stercoralis* applying the Baermann technique. Participants will be considered *T. trichiura* cured if no eggs have been found in the stool. EPG will be assessed by adding up the egg counts from the quadruplicate Kato-Katz thick smears and multiplying this number by a factor of six. Geometric and arithmetic mean egg counts will be calculated for the different treatment arms before and after treatment to assess the corresponding ERRs. The stool samples collected 21 days post-treatment for efficacy assessment will further be re-tested with the same rapid diagnostic test and immunoassay used at baseline to determine fecal occult blood and calprotectin levels. Frequencies of subjects found positive with either of the two markers and by intensity category for calprotectin will be calculated by treatment arm.

At the end of the study (*i.e.* for exclusive DF study participants 1 month post-treatment, for trial participants 12 months post-treatment) all participants remaining positive for *T. trichiura*, other soil-transmitted helminths or filariasis will be treated with albendazole-ivermectin, the currently best approved and recommended treatment against *T. trichiura* [29].

Parallel group multi-country study

Potential extended effects on follow-up helminth prevalences will be assessed using the same methodological approach as used for the efficacy assessment and will be based on stool samples collected 6 and 12 months post-treatment. Likewise fecal occult blood and calprotectin will be re-determined on the same stool samples.

To assess eventual reduction in morbidity and improvement in nutritional indicators all trial participants will be asked to provide another finger-prick at the 6 and 12 month follow-up for Hb measurement and rapid diagnostic testing (*i.e.* malaria and filariasis) and once more a venous blood sample for micronutrient/blood parameter evaluation at all three follow-up time points, respectively. Anthropometric measurement including height, weight, MUAC and skinfold thickness will be repeated on the same occasion. Children (6-16 years) will be asked to re-assess their own physical functioning in repeated questionnaire interviews during these two last follow-ups. Long-term satisfaction with the treatment will be asked 6 months post-treatment. Mean values for continuous outcomes and frequencies for binary/categorical outcomes will be calculated for each treatment arm and follow-up time point and compared using descriptive and repeated measurement analysis as detailed in section 7.3.

4.3.3 Pharmacokinetic studies

DF study

The micro-sampling device dried blood spot (DBS) is a more robust, ethical and patient-friendly technique compared to venous blood sampling to evaluate the pharmacokinetic profile of a drug. In order to use DBS in a clinical trial, it first needs to be evaluated that the analysis of venous and capillary blood yields same drug concentrations. Therefore, plasma and DBS samples were previously collected in two independent clinical trials in rural Côte d'Ivoire with adult volunteers who received either the standard dose of albendazole (400 mg) or the standard dose of ivermectin (200 µg/kg). Methods to extract and quantify ivermectin in the different matrixes have been validated and applied to the samples of the adult volunteers. Results show consistent correlation of plasma and DBS samples so that DBS can be reliably used.

The micro-sampling device DBS will be used as a tool to evaluate the pharmacokinetic (PK) parameters of albendazole and ivermectin in the DF study of their co-administration in school-aged children. 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 0, 1, 2, 3, 4, 5, 6, 7, 9, 24, 48 hours post-dosing. A few drops of blood will be transferred at each time point on DBS filter paper (Whatman) and dried for approximately 1 hour. The DBS cards will be transported to Basel and stored at -80° C until analysis. Albendazole and its metabolites will be quantified using a 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 3 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.

4.4 Measure to minimize bias

For each study (*i.e.* parallel group trial and DF study) independently study participants eligible for treatment will be randomly assigned to one of the treatment arms using a computer-generated stratified block randomization code. The random allocation sequence with varying random blocks of four or eight and stratified by 2 levels of baseline infection intensity (light: <1000 EPG, and moderate plus heavy: ≥ 1000 EPG *T. trichiura* infections) will be provided by a statistician. The treatment arms will have an equal number of participants with light infection intensity, although the number of light versus moderate/heavy infections are not expected to be equal in each arm, depending on the distribution of infection intensity in the recruited cohort. The parallel group trial will

be double blinded (*i.e.* study participants and the trial team/researchers conducting the treatment and assessing the outcomes will be blinded) using repacked tablets including appearance-matched placebos while the DF study will be single blinded (*i.e.* all outcome assessors except the investigators who provide the treatment and the study participants who get either active or placebo tablets matching in appearance will be blinded) due to the nature of this study (*i.e.* including ascending doses).

4.5 Study duration and duration of subject participation

The trial will last fourteen months. The screening for the baseline will start three weeks prior to the treatment. Follow-up screening will take place 14-21 days, 180 days and 360 days post-treatment and last each time for about three weeks. Schedules of visits are summarized below.

4.6 Schedule of visits

Parallel group multi-country study

Table 3. Schedule of visits of parallel group study.

	Screening -21 to -1 days	**Baseline/Treatment/Safety** Hours 0		3	24	**Follow up** Days 21	180	185	360
Diagnosis (stool examination)	X					X	X		X
Gut morbidity (stool RDTs)	X					X	X		X
Informed consent	X								
Demographics	X								
Medical history		X							
Clinical examination		X					X		X
Pregnancy testing		X					X		
Hemoglobin measurement		X					X		X
***Plasmodium* co-infection**		X					X		X
***Filaria* co-infection**		X					X		X
Venous blood examination		X				X	X		X
Physical functioning		X					X		X
Capturing AEs				X	X	X			
Capturing SAE				X	X	X			
Treatment satisfaction				X		X	X		

Randomization and treatment (spans Hours 0 through 24)

Selective re-treatment (spans Days 185 through 360)

DF study

The general outline of the DF study is similar to the parallel group multi-country study with the following adaption: Follow-up will be performed 21 days after treatment only and micro-blood sampling will be performed 0–48 hours post treatment.

Table 4. Schedule of visits of dose-finding study.

	Screening					**Follow up**
	-21 to -1 days	Hours 0	Randomization and treatment	1-9	24	48	21 days
Diagnosis (stool examination)	X						X
Informed consent	X						
Demographics	X						
Medical history		X					
Clinical examination		X					
Rapid diagnostic tests		X					
PK sampling		X		X	X	X	
Capturing AEs				X (3h)	X		X
Capturing SAE				X (3h)	X		X

5. Selection of the trial subjects

5.1 Recruitment

The study will be carried out in community members aged 6–60 years in areas with moderate to high *T. trichiura* endemicity (communities with a prevalence ≥ 25%) identified from earlier studies and/or based on experience of the local collaborating teams. The trial will be implemented as community-based study in order to recruit participants from a broad age range (6–60 years). Ideally, entire communities with a population size of < 1000 inhabitants will be included in the study for pre-screening and identification of *T. trichiura* cases to avoid potential selection bias of households. To identify all potentially eligible households of the respective communities and its composition in terms of age groups a preceding population census will be conducted.

All adult community members, including parents/caregivers of minor participants, will be invited to participate in an information meeting to explain the purpose and procedures of the study, including potential benefits and risks. Parents/caregivers/potential participants will be encouraged to ask questions in an open discussion forum. During this session, they will be informed of preventive actions they can take to help protect their children from acquiring *T. trichiura* and other STH infections in the future (*e.g.* adequate food, preparation and defecation behavior).

Those parents/caregivers and their children 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. Written informed consent signed by either the participant him/herself (≥21 years of age) or by parents and/or caregivers for children/adolescents; and written assent by child/adolescent (aged 6–20 years).

2. Agree to comply with study procedures, including provision of two stool samples at the beginning (baseline) and on three follow-up assessments (approximately 3 weeks, 6 months, and 12 months later).
3. Aged ≥6 to ≤60 years for parallel group trial and ≥6 to ≤12 years for DF study.
4. At least two slides of the quadruple Kato-Katz thick smears positive for *T. trichiura* and infection intensities of at least 100 EPG.

5.3 Exclusion criteria

1. No written informed consent by individual/parents and/or caregiver.
2. Presence of major systemic illnesses, *e.g.* severe anemia (below 80 g/l Hb according to WHO [30]), clinical malaria as assessed by a medical doctor (positive *Plasmodium* RDT and ≥38 °C ear temperature), upon initial clinical assessment.
3. History of acute or severe chronic disease (*e.g.* cancer, diabetes, chronic heart, liver or renal disease).
4. Recent use of anthelmintic drug (within past 4 weeks).
5. Attending other clinical trials during the study.
6. Negative or low egg count (less than 100 EPG or less than 2 out of 4 slides positive) diagnostic result for *T. trichiura* eggs in the stool.
7. Known allergy to study medications (*i.e.* albendazole and ivermectin).
8. Pregnancy or lactating in the 1st week after birth (according to WHO guidelines within LF control programs [31]).
9. Currently taking medication with known interaction (*e.g.* for albendazole: cimetidine, praziquantel and dexamethasone; for ivermectin: warfarin).

5.4 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 a participant withdraws).

2. At the discretion of the Principal Investigator (PI) or co-PI, if the participant is not compliant to the requirements of the protocol.

Discontinued 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.

5.5 Treatment of subjects

Parallel group multi-country and DF study

All *T. trichiura*-infected, consenting, and participating community members will be treated with the respective single or combination treatment regimen at day 0. 400 mg albendazole will be the product of Glaxo Smith Kline (Zentel®) and a single tablet administered. 3 mg tablets of ivermectin (Stromectol®) will be obtained from Merck, France, the weight recorded for each participant and the correct dose evaluated and administered. Matching ivermectin placebo tablets (in terms of appearance) will be produced and a certificate of manufacture and analysis be provided by the University of Basel. The tablets for the main trial, which is double-blinded, will

be repacked into neutral separate plastic bags each containing one albendazole tablet and the maximum number of ivermectin tablets with regard to weight and dose or the corresponding number of placebo tablets. The ivermectin tablets for the dose-finding study will be kept in the original package until treatment day. Since albendazole and ivermectin are known to be better absorbed in humans after a high-fat meal was consumed, participants will receive a local high-fat breakfast (sandwich with *e.g.* oily sardines) prior to treatment [32, 33].

All drugs will be administered in the presence of the investigator(s), 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. The Principal Investigator 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.

Antimalarial treatment (*i.e.*, artemisinin-based combination therapy) will be provided to participants found with clinical malaria (*i.e.* positive *Plasmodium* RDT and ≥38 °C ear temperature) or severely anemic in combination with a positive RDT result. Iron supplementation will be offered to severely anemic individuals with a negative RDT result.

To avoid interference of potential on-going control programs against helminthiases with the infection status of the trial participants, communication with local stakeholders will be established to ascertain that trial participants will not undergo MDA treatment. Missed-out rounds of planned MDA against helminthiases in study participants will be substituted with a free single-dose treatment (*i.e.* albendazole 400 mg + ivermectin 200 µg/kg) against STH, *S. stercoralis* as well as *Filaria* infection at the study endpoint (after the day 360 follow-up assessment) offered by the study team. At each follow-up time point, participants will be interviewed whether they had taken any anthelmintic treatment (e.g. self-purchased, obtained from clinics etc).

5.6 Concomitant therapy

All medications taken one month before and during the study period until the last stool examination must be recorded with indication, dose regimen, date and time of administration.

Medication(s)/treatment(s) permitted during the trial:

- Analgesics and antipyretics are allowed to be given to the subjects in case of fever, antiemetics to prevent nausea and vomiting and/or antibiotics to prevent or treat bacterial superinfection.

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

- No other active drugs against helminths are permitted during the trial.

- No drugs with known interactions with the study medication are permitted during the trial.

6. Safety assessments

Few AEs have been reported following ivermectin-albendazole co-administration in STH-infected individuals. The most common AEs were abdominal cramps, headache, fatigue, nausea, diarrhea, fever and vertigo [7, 8, 34]. The safety profile of co-administered ivermectin and albendazole will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs and a physical, clinical and biochemical examinations.

6.1 Adverse event definitions

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

a) Any unfavorable and unintended signs, symptoms or disease temporally associated with the use of a medicinal product, whether or not considered related to the condition under study and the study product;

b) Any abnormality detected during physical examination.

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

The observation time for AEs starts when the treatment is initiated until day 21 (3 weeks after last drug administration).

These data will be recorded on the appropriate case report form (CRF) sections, regardless of whether they are thought to be associated with the study or the drug under investigation. Associated with the use of the drug means that there is a reasonable possibility that the event may have been caused by the drug (see also relatedness definitions below).

6.1.1 Severity grading

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

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

6.1.2 Relatedness

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

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

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

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

6.1.3 Expectedness

Expected adverse drug reaction: Any AE possibly related to the co-administration of ivermectin-albendazole reported in the literature or on the drug package leaflets and listed in the consent form.

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

6.1.4 Serious adverse events

According to the ICH "Clinical Safety Data Management: Definitions and standards for expedited Reporting E2A" [35], a serious adverse event (SAE) includes any event (experience) or reaction in any untoward medical occurrence that at any dose:

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

A "severe" AE does not necessarily meet the criteria for a "serious" AE. SAEs are reported from consent to 3 weeks post-treatment (Day 21).

SAEs that are still ongoing at the end of the study period will be followed up to determine the final outcome.

The causality of any SAE that occurs after the study period and its possible relatedness to the study treatment or study participation will also be assessed by investigators as described in section 6.1.2.

6.1.5 Suspected unexpected serious adverse reactions

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

6.2 Methods of recording and assessing adverse events

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, physical and biochemical 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 also be interviewed 3 and 24 hours and again 3 weeks after treatment about the occurrence of AEs (see chapter 4.6).

Information on all AEs (onset, duration, intensity, seriousness and causality) will be immediately entered in the appropriate AE module of the CRF that serves as 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 and iii) an assessment of intensity of AEs will be judged by the study physician.

All SAEs or SUSARs must be reported as described in Section 6.3.

6.3 Reporting of serious adverse events

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

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

6.4 Safety reporting to Health Authorities and 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 'Ethikkomission Nordwest- und Zentralschweiz' (EKNZ, Switzerland), the ethics committee and the 'Direction de la Pharmacie, du Médicament et des Laboratoires (DPML)' in Côte d'Ivoire according to national rules. Fatal or life-threatening SAEs or SUSARs will be reported within 24 hours followed by a complete report within 7 additional calendar days. Other SAEs and SUSARs that are not fatal or life-threatening will be filed as soon as possible but no later than 14 days after first knowledge by the sponsor.

7. Statistics

7.1 Definition of primary endpoint

CR of co-administered ivermectin-albendazole against *T. trichiura* is the primary endpoint in our study. Since treatment success is influenced by infection intensity, stratified block randomization will be used (baseline infection intensity: light infections and moderate/heavy infections) to ensure balanced treatment groups in terms of infection intensity.

7.2 Justification of number of trial subjects

Parallel group multi-country study

Based on available summarized efficacy measures from a recent review [1] and the published literature, we assume that the CR of albendazole against *T. trichiura* is 30% compared to 50% in the albendazole-ivermectin treatment regimen. To detect a difference with 90% power at a two-sided 5% significance level, we require 121 participants per study arm and 143 to account for potential loss to follow-up of 15%. We further assume the same treatment efficacy in the mid-term treatment and a 6-months reinfection risk of 10%. Consequently we expect a proportion of negative patients after 12 months of 44% in the albendazole arm and of 65% in the albendazole-ivermectin arm resulting in a required sample size of 111 participants per arm. To account for a loss to follow-up of 30% after 6 months and 40% at final assessment (12 months) we aim to recruit 300 participants in each treatment group (600 in total) in each country.

Subgroup analysis will be conducted stratifying the study population by age category (school-aged and adults). For the subgroup analysis we will pool the data from all 3 countries to ensure sufficient statistical power.

DF study

Since the existence of a drug effect is well known, the main aim of the study is the elucidation of the nature of the dose–response relationship. Modeling approaches showed that with 40 children enrolled in each of the 4 study arms (placebo, 200 µg/kg, 400 µg/kg, and 600 µg/kg co-administered with albendazole (400 mg)) the dose response prediction model had a median precision (one half length of the 95%-confidence intervals) of 10% assuming associated cure rates of 2.5%, 50%, 60% and 70% taking into account a loss to follow up of 10%. The suggested sample size is also in line with the recommendations from *Klingenberg et al. 2009* [36]. This sample size is sufficiently high to determine the key PK parameters as well as pharmacokinetic/pharmacodynamic (PK/PD) relationships taking into account that PK variability is high.

7.3 Description of statistical methods

The primary available case analysis will include all participants with primary end point data. In addition, an intention-to-treat analysis will be conducted considering all participants with missing endpoint data as treatment failure or all as treatment success to ensure that the results are not sensitive to potential loss to follow-up bias. CRs will be calculated as the percentage of egg-positive (larvae- positive for *S. stercoralis*) participants at baseline who become egg-negative (larvae-negative) after treatment. EPG will be assessed by adding up the egg counts from the quadruplicate Kato-Katz thick smears and multiplying this number by a factor of six. For *S. stercoralis* infection no further quantification of larvae in stool will be done. The ERR of STH infection will be calculated as:

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

In the primary model we estimate the difference among CRs by using unadjusted logistic regressions. In a subsequent analysis an adjusted logistic regression (adjustment for age, sex and weight) will be performed.

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

Results from the stool RDT for fecal occult blood will be categorized as negative, trace and positive. For calprotectin, individuals with levels exceeding 50 µg/g will be considered as positive and concentrations be classified into low (51–149 µg/g), medium (150–299 µg/g) and high (≥300 µg/g) intensity [16].

Anthropometric measurements such as height and weight of school-aged children will be translated into weight-for-age, height-for-age and weight-for-height related z-scores using readily available Stata macros calculating growth indicators for children 5-19 years [37]. Body mass index and indicators for muscle and fat tissue such as MUAC and skinfold thickness will serve as additional indicators of nutritional status for adults and will further be classified using a percentiles approach to compare within populations [38].

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 [25].

Nutritional and morbidity indicators will be analysed using logistic and linear regression as appropriate. To compare individual's changes in nutrition/morbidity categories as an effect from treatment McNemar's test will be applied. The analysis after 6 and 12 month of follow-up will be complemented by generalized estimating equation (GEE) models with independent correlation structure and empirical estimators to account for missing data.

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

On the basis of the LC-MS/MS measurements, the following PK parameters for plasma 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 infinity

$T_{1/2}$ elimination half-life

T and AUC above minimal inhibitory concentration (MIC)

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.

Further PK analysis will be undertaken fitting a structural compartmental PK model with the software NONMEM 7 [39] via nonlinear mixed effects modeling (allowing for both between patient variation and random effects). This model will describe the plasma drug levels in time, allowing one to investigate variation between patients in drug levels. In addition, PK/PD analysis will be undertaken via NONMEM to investigate the drivers of cure and/or burden reduction and potentially any covariates with drug levels.

7.4 Description of data management and data quality control

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

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

1. Eggs counts of *T. trichiura*, *A. lumbricoides* and hookworm and infection status with *S. stercoralis* based on participants' stool samples analyzed using the Kato-Katz and Baermann technique, respectively, before (baseline) and at 3 time points after treatment (follow-ups after 3 weeks, 6 and 12 months). Presence of fecal occult blood and elevated calprotectin levels will be evaluated and recorded applying RDTs on the same stool samples and assessment time points.
2. Personal information such as name, age, gender and household composition of trial participants.
3. Anthropometric and clinical characteristics of the trial participants collected using the study's CRF such as weight, height, skinfold thickness, blood pressure, temperature, hemoglobin level, infection status with *Plasmodium spp*. and filariasis, any abnormal medical condition or chronic disease as well as pregnancy in female participants 10 years and above.
4. Number and type of AEs registered in the CRF actively probed for 3 and 24 hours after treatment. The same data will be collected during the collection of the first sample at the 3-week follow-up.
5. Scales for participant-rated treatment satisfaction and self-rated physical functioning in school-aged children captured on different time points (i.e. 3 weeks and 6 months and baseline, 6 and 12 months after treatment, respectively) and recorded on the CRF.
6. Concentration levels of blood and biochemical parameters together with indicators for micronutrient status before (baseline) and at 3 time points after treatment (follow-ups after 3 weeks, 6 and 12 months).
7. Household-level data on socioeconomic characteristics, presence and use of water and sanitation as well as hygiene-related attitudes and practices.

All data on parasitology and questionnaires about AEs, self-reported clinical signs and symptoms, physical functioning, and treatment satisfaction will be paper-captured and subsequently doubled entered (data entry SOP) into ACCESS data entry masks by two independent persons. For quality assurance error, range and consistency checks will be programmed for the ACCESS data entry masks and all double-entered data be cross-checked using the Data Compare utility of EpiInfo. Any discrepancies will be corrected by consulting the hard copy.

Data in category 1 to 6 will be double-entered using an EpiInfo mask and saved in .mdb, .xlsx, .dta, and .csv. Data in category 7 will be directly entered while collecting into tablets using Open Data Kit (free electronic data collection software) and uploaded to a server hosted at Swiss TPH. All categories will be merged into a single master file saved in .dta, .xlsx and .csv. Data will then be analysed as described in section 7.3. Hard copies of the data collected within the trial country such as parasitological, stool RDT, blood parameter sheets and CRFs will remain at Centre Suisse de Recherches Scientifiques en Côte d'Ivoire (CSRS). 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 CSRS. All data is expected to not exceed 5GB.

Invited and screened patients will be listed in a confidential "subject identification list and 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 pseudonymised data and will only be accessible to the local principal investigator. All study-specific data will only contain this unique identifier instead of any names. Electronic data files will be stored on secured network drives with restricted access for study personnel only. Data analysis will be conducted with pseudonymised data and reporting of findings will be fully anonymised. All databases will be password secured.

Essential infrastructure such as lockable cabinets for safe storage of hardcopy data will be made available. Network drives with restricted access for authorized personnel only and appropriate analysis software are available.

8. Duties of the investigator

8.1 Investigator's confirmation

This trial will be conducted in accordance with the protocol, International Conference on Harmonization Good Clinical Practice E6 (R2) (ICH-GCP) and the current version of the Helsinki Declaration.

All protocol modifications must be documented in writing. A protocol amendment can be initiated by either the Sponsor/PI or any Investigator. The Investigator will provide the reasons for the proposed amendment in writing and will discuss with the Sponsor/PI and Co-PIs. Any protocol amendment must be approved and signed by the Sponsor/PI and must be submitted to the appropriate Independent Ethics Committee (IEC) for information and approval, in accordance with local requirements, and to regulatory agencies if required. Approval by IEC must be received before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial 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) and patient liability insurances will be issued in the respective trial countries.

8.3 Project management

The trial team will include the PI (Prof. Jennifer Keiser), three Co-PIs (Dr. Eveline Hürlimann, Dr. Jessica Schulz, and Dr. Jean Coulibaly), a trial statistician (Dr. Jan Hattendorf), as well as a local physician (Dr. Yves Koutouan N'Gbesso), nurses and laboratory technicians. Prof. Jennifer Keiser, Dr. Eveline Hürlimann, Dr. Jessica Schulz and a PhD student will be responsible for staff management, communication with the collaborative group, recruitment monitoring, data management, safety reporting, analysis, report writing and dissemination of the trial results. Dr. Jean Coulibaly and the PhD student will monitor all field activities at the study site. Dr. Yves Koutouan N'Gbesso, will be responsible for patient recruitment, medical aspects of the trial and enrolment of patients in the trial.

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

The study will be submitted for approval by the institutional research commission of the Swiss TPH and the ethics committees of Switzerland (EKNZ: Ethical Commission of northwest/central Switzerland) and Côte d'Ivoire (CNER: Comité Nationale d'Ethique de la Recherche) and the Ivorian medicines regulatory authority (DPML: Direction de la Pharmacie, du Médicament et des Laboratoires). The study will be undertaken in accordance with the Declaration of Helsinki and GCP.

9.2 Evaluation of the risk-benefit ratio

Ivermectin in combination with albendazole are well-known, widely used drugs in mass treatment programs against filariasis, and have little and mainly mild AEs (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 *T. trichiura* will be treated with ivermectin (200 µg/kg)-albendazole (400 mg) considering higher efficacy compared to the existing standard treatment (albendazole monotherapy) and recent inclusion as recommended treatment scheme on the Essentials Medicines List [29].

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 parents or caregivers of eligible children and all adult participants (≥21 years) will be individually informed about benefits and risk associated to the trial. They will have sufficient time for reflection of their child's or their own participation, respectively. 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. In addition to a written informed consent form signed by their parent or caregiver, minor participants (aged 6-20 years) will also be briefed verbally and written assent sought

in form of their name written down or if illiterate by providing a thumb print. Even if the minor participant gives written assent, the parent/caregiver has to sign the consent.

Information sheets are printed in French but will additionally be verbally translated into local languages (*i.e.* Abbé, Attié, Dioula, Moré) during community meetings. To all participants and parents/caregivers 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.

9.4 Subject confidentiality

The obtained data will be handled strictly confidentially. Only members of the study team will have access to the data. Personal data will be coded for data analysis. The codes will be filled with the participant's identity on a separate file (subject identification list and screening log) and stored in a secured place at the local institutions (*i.e.* Côte d'Ivoire: CSRS, Lao PDR: National Institute of Public Health, and Pemba: Public Health Laboratory Ivo de Carneri) and will only be accessible to investigators. 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. 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 include school-aged children, since *T. trichiura* infection occurs often in children; hence this age group is at high risk of infection and is therefore the major target group in MDA campaigns. Pharmacokinetic and DF studies in this population, however, have to our knowledge so far only been done or are underway by the research team itself for the investigated medicine products (*i.e.* ivermectin and albendazole). Since PK parameters vary between children and adults these studies cannot be obtained by carrying out the trial on adults. Our trial will produce more evidence to support the search for a safe and effective treatment scheme against STH infections in children and whole communities.

9.6 Other aspects

Within the DF study one study arm will include school-aged children treated with placebo. However, this group will be treated with a single dose of co-administered albendazole (400 mg) and ivermectin (200µg/kg), as meanwhile listed on the EML of WHO to treat STH infection [29], at the first follow-up (already 3–4 weeks later). 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 3-weeks delay in treatment should not cause any medical concern for the participants of the placebo arm. 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. Quality control and quality assurance

10.1 Monitoring and auditing

We will work with locally based monitors. These will conduct site visits to the investigational facilities for the purpose of monitoring the study. Details will be described in a separate monitoring plan. The investigator will permit them access to study documentation and the clinical supplies dispensing and storage area. Monitoring

observations and findings will be documented and communicated to appropriate study personnel and management. A corrective and preventative action plan will be requested and documented in response to any audit observations. No sponsor initiated audits are foreseen, but audits and inspections may be conducted by the local regulatory authorities or ethics committees. The Investigator agrees to allow inspectors from regulatory agencies to review records and is encouraged to assist the inspectors in their duties, if requested.

10.2 Access to data, handling of data and samples (data protection), archiving (place, duration) and destruction

Information about study subjects will be kept confidential and managed accordingly. A paper 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 results of the research study will be published, but subjects' names or identities will not be revealed. Records will remain confidential. To maintain confidentiality, the Sponsor-Investigator will keep records in locked cabinets and the results of tests will be coded to prevent association with participant's names. Data entered into the ACCESS data entry mask will be accessible only by authorized personnel directly involved with the study and will be encoded. Subject-specific information may be provided to other appropriate medical personnel only with the subject's permission for adults or the parent/caregiver's permission for minors.

After the study has been completed all samples will be destroyed and research data and related material will be kept 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. Storage and backup will be in three places: personal laptops of Jennifer Keiser, Eveline Hürlimann, Jessica Schulz, Chandni Patel and Jean Coulibaly, Swiss TPH shared server and SWITCHdrive (a cloud storage supported by University of Basel). Archiving conditions will be made strictly confidential by password protection.

10.3 Data entered directly in the CRF – definition of source data

Source Data are the clinical findings and observations, laboratory data maintained at the study site. Source data are contained in **source documents**. Local authorities are allowed to access the source data. Data will be entered directly onto the CRFs. The CRF is considered as a source document. All CRFs will be kept for at least 15 years.

The study site will retain the original 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.

10.4 Data and safety monitoring board / data monitoring committee

In our study no data and safety monitoring board will be established, since we work with well-known drugs in a limited number of participants and using a single dose treatment. This study is anticipated to be no greater than minimal risk to participants.

10.5 Study Documents: Translations - Reference language

- 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.

11. Dissemination of results and publication

The final results of this study will be published in a scientific journal and presented at scientific conferences. The Bill & Melinda Gates Foundation will be acknowledged as study funder. All results from this investigation are considered confidential and shall not be made available to any third party by any member of the investigating team before publication. A study report will be shared with the local ethics committees and the national regulatory authorities.

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6. Trial protocol Laos:

Efficacy and safety of ivermectin and albendazole co-administration in school-aged children and adults infected with *Trichuris trichiura*: a multi-country randomized controlled trial

Protocol Number	1		
Version Number	1.01	**Document Date**	14.06.2018
Sponsor Contact	Prof. Dr. Jennifer Keiser, Swiss Tropical and Public Health Institute, Tel.: +41 61 284-8218 Fax: +41 61 284-8105 E-mail: jennifer.keiser@unibas.ch		
Principle Investigator	Prof. Dr. Jennifer Keiser, Swiss Tropical and Public Health Institute, Tel.: +41 61 284-8218 Fax: +41 61 284-8105 E-mail: jennifer.keiser@unibas.ch		
Funding Agency	Bill and Melinda Gates Foundation		

1. General information

I. List of investigators and other persons involved

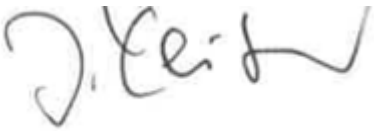
Title	Names	Institution	Position	Function in trial
Prof. Dr.	Jennifer Keiser	Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland	Unit head	Principal Investigator
Dr.	Eveline Hürlimann	Swiss TPH	Postdoc	Co-PI
Dr.	Somphou Sayasone	Lao Tropical and Public Health Institute (Lao TPHI) Vientiane, Lao PDR	Group leader / Study physician	Co-PI
Dr.	Jan Hattendorf	Swiss TPH	Project leader	Statistician

II. Signatures

Statistician

Signature		Date of Signature 14.06.2018
Name	Jan Hattendorf	
Title	Dr.	
Institution	Swiss Tropical and Public Health Institute	
Address	Department of Medical Parasitology and Infection Biology Swiss Tropical and Public Health Institute, Socinstr. 57	
Phone	+41 61 284-8193	

Principal investigator

Signature		Date of Signature 14.06.2018
Name	Jennifer Keiser	
Title	Prof.	
Institution	Swiss Tropical and Public Health Institute	
Address	Department of Medical Parasitology and Infection Biology Swiss Tropical and Public Health Institute, Socinstr. 57	
Phone	+41 61 284-8218	

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-Principal investigator

Signature		Date of Signature 14.06.2018
Name	Eveline Hürlimann	
Title	Dr.	
Institution	Swiss Tropical and Public Health Institute	
Address	Department of Medical Parasitology and Infection Biology Swiss Tropical and Public Health Institute, Socinstr. 57	
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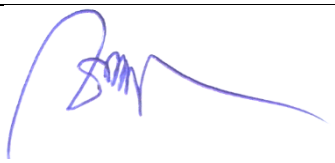
Co-Principal investigator

Signature		Date of Signature 14.06.2018
Name	Somphou Sayasone	
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III. Abbreviations

AE	Adverse event
CI	Confidence interval
CR	Cure rate
CRF	Case report form
EKNZ	Ethikkomission Nordwest- und Zentralschweiz
EML	Essential medicine list
EPG	Eggs per gram
ERR	Egg reduction rate
GCP	Good clinical practice
GEE	Generalized estimating equation
Hb	Hemoglobin
ICH	International council for harmonization of technical requirements for pharmaceuticals for human use
IEC	Independent ethics committee
Lao TPHI	Lao Tropical and Public Health Institute
MDA	Mass drug administration
MUAC	Mid-upper arm circumference
PC	Preventive chemotherapy
PCR	Polymerase chain reaction
PI	Principal investigator
RDT	Rapid diagnostic test
SAE	Serious adverse event
SOP	Standard operating procedure
STH	Soil-transmitted helminth
Swiss TPH	Swiss Tropical and Public Health Institute
SUSAR	Suspected unexpected serious adverse reaction
WHO	World Health Organization

IV. Synopsis

Sponsor/Sponsor-Investigator	Prof. Dr. Jennifer Keiser
Study Title	Efficacy and safety of ivermectin and albendazole co-administration in school-aged children and adults infected with *Trichuris trichiura*: a multi-country randomized controlled trial
Short title	Efficacy and safety of IVM/ALB co-administration
Protocol Number, Date and Version	1, 13.06.2018, v1.01
Trial registration	Has been registered on ClinicalTrials.gov (reference: NCT 03527732)
Clinical phase	Phase 3 trial
Sample size	1800 (600 participants in each of 3 settings)
Indication	*Trichuris trichiura* infection (eggs in stool)
Investigational Product and Reference Treatment	Ivermectin and albendazole
Study Rationale	To provide evidence on potentially enhanced efficacy by combining the standard drug albendazole with ivermectin in school-aged children and adults against infection with *T. trichiura*.
Study Objectives	To compare the efficacy and safety of standard doses of co-administered ivermectin (200 µg/kg) and albendazole (400 mg) compared to albendazole (400 mg) alone in community members aged 6-60 years. Our **primary objective** is to comparatively assess the efficacy in terms of cure rates (CRs) against *T. trichiura* infections among school-aged children and adults of the following oral treatment regimens: • Albendazole (400 mg)/ivermectin (200 µg/kg) combination • Albendazole (400 mg) monotherapy

	The **secondary objectives** of the trial are: a) To evaluate the safety and tolerability of the treatment regimens b) To compare the egg reduction rate (ERR) of the treatment regimens against *T. trichiura* c) To determine the CRs and ERRs of the drugs in study participants (6-60 years) infected with hookworm, *Ascaris lumbricoides* and *Strongyloides stercoralis* d) To investigate potential extended effects on follow-up helminth prevalences (6 and 12 months post-treatment) of the two treatment regimens (as assessed among participants with cleared infection on days 21 and 180) e) To compare CRs based on infection status determined by novel polymerase chain reaction (PCR)-based and standard microscopic diagnosis f) To assess potential differences in susceptibility to the treatment regimen between the hookworm species, *Necator americanus*, *Ancylostoma duodenale* and *A. ceylanicum*, as classified through the novel PCR-based diagnosis g) To characterize *T. trichiura* strains from different epidemiological settings and investigate potential resistance markers using a deep sequencing analysis h) To determine optimal timing for measuring anthelmintic efficacy in *T. trichiura* infection i) To evaluate potential benefits from deworming on morbidity indicators, microbiome and nutritional parameters
Study design	Double blind, randomized controlled trial
Study product / intervention	Administration of a single oral dose of ivermectin + albendazole
Comparator(s)	albendazole (400 mg) monotherapy
Key inclusion / Exclusion criteria	**Inclusion:** School-aged children and adults (6-60 years) infected with *T. trichiura* with at least two slides of the quadruple Kato-Katz thick smears positive and infection intensities of at least 100 eggs per gram of stool (EPG), agreeing to comply with study procedures, including provision of two stool samples at the beginning (baseline) and on three follow-up assessments (approximately 3 weeks, 6 months, and 12 months later), written informed consent signed by parents and/or caregivers for children/adolescents; and oral assent by child/adolescent (6-17 years).

	Exclusion: No written informed consent by individual/parents and/or caregiver, below age of 6 years and weight of 15 kg, any clinically relevant abnormality (including severe anemia or clinical malaria) or history of acute or severe chronic disease (*e.g.* cancer, diabetes, chronic heart, liver or renal disease), recent use of anthelminthic drug (past 4 weeks), attending other clinical trials during study, negative diagnostic or low egg count (less than 100 EPG or less than 2 out of 4 slides positive) result for *T. trichiura*, known allergy to study medication, pregnancy or lactating in the 1st week after birth, taking medication with known interaction on study drugs.
Primary Endpoints	*T. trichiura* infection status assessed by Kato-Katz 14-21 days after treatment
Secondary Endpoints	• ERR against *T. trichiura* • CRs and ERRs against *A. lumbricoides*, hookworm and *S. stercoralis* • Adverse events • Infection status assessed by PCR
Exploratory Endpoints	• Molecular characterization and resistance markers of *T. trichiura* • Optimal timing for drug efficacy assessment in *T. trichiura* infection • Nutritional and microbiome status • Morbidity indicators
Interim Analyses	None
Study Duration	14 months
Schedule	06/2018 of first-participant in (planned) 08/2019 of last-participant out (planned)
Study centres	Multinational study with trial sites in Côte d'Ivoire, Lao PDR and Pemba Island (Tanzania)
Measurements & procedures	Two stool samples (each of a minimum of 15 grams) will be collected if possible on two consecutive days or otherwise within a maximum of 5 days. During collection of the second stool sample participants will be asked to provide a urine sample (minimum 10 ml) additionally. The medical history of the participants will be assessed with a standardized questionnaire, in addition to a clinical examination carried out by the study physician before treatment. All participants will also be interviewed before treatment, 3 and 24 hours and 3 weeks after treatment about the occurrence of adverse events. Children aged 6-16 years will additionally be asked to rate their own physical functioning by replying to a pre-tested questionnaire at baseline and 6 and 12 months after treatment. The efficacy of the treatment and potential extended effects on

	follow-up prevalence will be determined 14-21 days, 6 months and 12 months post-treatment by collecting another two stool samples. Subjective treatment satisfaction will be assessed 3 hours, 3 weeks and 6 months after treatment to investigate relationship with treatment compliance and observed efficacy in reducing egg output and morbidity. All stool samples will be examined with duplicated Kato-Katz thick smears for *T. trichiura*, *A. lumbricoides* and hookworm. *S. stercoralis* infections will be identified using the Baermann technique and recorded qualitatively as larvae-positive or negative. ~~Complementary to stool-based diagnostics, a small portion of urine from each participant will be fixed, transferred to a laboratory at Khon Kaen University in Thailand and examined for antibodies of *S. stercoralis* using a newly developed ELISA-based assay.~~ For subsequent PCR and microbiome analysis of the stool samples a portion of 1.5-2 g from each specimen will be frozen and preserved in 70% ethanol, respectively and shipped to a reference laboratory at Swiss TPH in Switzerland. At baseline and in the first follow-up (3 weeks post treatment) an additional portion of stool (1.5-2 g) from a subsample of 10 participants identified with heavy intensity infections in each case and study setting will be preserved in 95% ethanol, shipped to the same reference laboratory and subjected to deep sequencing for characterization of *T. trichiura* strains and investigation of potential resistance markers. Fecal occult blood and calprotectin in stool as markers for gut morbidity and inflammation will be detected using a rapid diagnostic test and an immunoassay, respectively. A subsample of 30 participants will be asked to provide a daily stool sample for a period of up to 4 weeks to monitor dynamics of *T. trichiura* egg output for subsequent determination of the optimal timing for drug efficacy assessment. Individuals found *T. trichiura* positive 6 months after baseline will receive a second round of treatment according to their group scheme. Each participant will be asked to provide a finger-prick blood sample for hemoglobin measurement and a rapid diagnostic test (RDT) for *Plasmodium* spp. at baseline and 6 and 12 months after treatment. At the same time points anthropometric measurements (*i.e.* height, weight, mid-upper arm circumference (MUAC) and skinfold thickness) will be taken for all participants. In addition, a venous blood sample (~8 ml) will be taken from each participant to assess biochemical blood parameters as proxies for vital organ functioning (*e.g.* complete blood count, urea, creatinine, transaminases etc.) measured in Laos and nutritional indicators for micro- (*i.e.* (pro-) vitamins, inflammation markers, and iron/ferritin) and macronutrient (*i.e.* albumin) deficiencies (evaluated in Switzerland) at baseline, day 21, day 180 and day 360. To all participating households (to any adult household member, ideally the household head), a household questionnaire will be administered assessing information on socioeconomic characteristics and access to sanitation, water facilities, and hygiene behavior.
Statistical Analyses	An available case analysis 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 egg-positive subjects at baseline who become egg-negative after treatment. Differences among CRs

	(between treatment arms and between diagnostic approaches) will be analysed by using crude and adjusted logistic regression modeling (adjustment for age, sex, and weight). Geometric and arithmetic mean egg counts will be calculated for the different treatment arms before and after treatment to assess the corresponding ERRs. Bootstrap resampling method with 5,000 replicates will be used to calculate 95% confidence intervals (CIs) for differences in ERRs. Further secondary outcomes – as nutritional and morbidity indicators - will be analysed using logistic and linear regression as appropriate. To compare individual's changes in nutrition/morbidity categories as an effect from treatment McNemar's test will be applied. The analysis after 6 and 12 month of follow-up will be complemented by generalized estimating equation (GEE) models with independent correlation structure and empirical estimators to account for missing data.
GCP statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ICH-GCP E6 (R2) as well as all national legal and regulatory requirements.
Key explanation for the inclusion of children	This study will involve school-aged children, since an infection with *T. trichiura* occurs most often in children and they are further the main target group of deworming campaigns.
Recruitment procedure	The parallel group trial will be conducted as a multi-country study with two settings in Africa and one in Asia recruiting each 600 community members: • West African setting: Côte d'Ivoire • East African setting: Pemba (Zanzibar, Tanzania) • Asian setting: Lao PDR The studies will be conducted in areas with moderate to high *T. trichiura* endemicity (communities with a prevalence ≥ 25%) identified from earlier studies and/or based on experience of the local collaborating teams. They will be implemented as community-based studies in order to recruit participants from a broad age range (6-60 years). Ideally, entire communities with a population size of < 1000 inhabitants will be included in the study for pre-screening and identification of *T. trichiura* cases to avoid potential selection bias of households. To identify all potentially eligible households of the respective communities and its composition in terms of age groups a preceding population census will be conducted.
Coverage of damages	Winterthur Police Nr. 4746321, trial insurance in Lao PDR: to be issued

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.

2. Background information

Albendazole and mebendazole are the most widely used drugs for preventive chemotherapy (PC) campaigns against soil-transmitted helminth (STH) infections. Albendazole is characterized by high cure rates (CRs) and egg reduction rates (ERRs) against infections with *Ascaris lumbricoides* (95.7% and 98.5%) and hookworm infections (79.5 and 89.6%). Lower efficacy is observed against *Trichuris trichiura* infections (CR 30.7%, and ERR of 49.9%) [1].

Therapies combining two or more drugs are widely advocated in different therapeutic areas such as tuberculosis, malaria, HIV/AIDS or cancer. The underlying rationale for multifactorial pharmacological treatment varies with the disease and includes the protection against the selection of drug-resistance, and hence, a prolongation of the life-span of effective and available drugs, and to increase and broaden the efficacy over drugs being administered in mono-therapy [2].

A recent review and meta-analysis found that ivermectin co-administered with albendazole is highly efficacious for the treatment of *T. trichiura* and is comparatively more efficacious than albendazole alone (Figure 1) [3]. Efficacy of ivermectin and albendazole against *A. lumbricoides* and hookworm are comparable and in some cases more efficacious than albendazole alone. Summarized efficacy measures of albendazole, mebendazole, and ivermectin against trichuriasis from a recent review [1] and earlier trials [4, 5] are shown in Table 1.

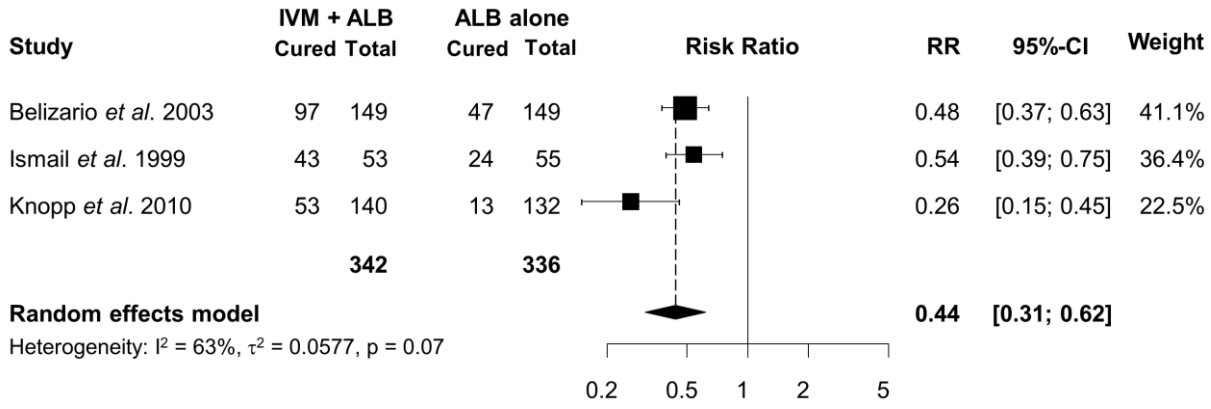

Figure 1. Forest plot displaying the results of a random-effects meta-analysis of the effect of the co-administration of albendazole-ivermectin on the number of patients infected with *T. trichiura* compared to albendazole alone.

Table 1. Average CRs and ERRs of albendazole and mebendazole for *T. trichiura* from a recent review [1] as well as findings from studies investigating ivermectin [4, 5]

Drug	CR (%)	95% CI	ERR (%)	95% CI
Albendazole	30.7	(21.0, 42.5)	49.9	(39.0, 60.6)
Mebendazole	42.1	(25.9, 60.2)	66.0	(54.6, 77.3)
Ivermectin	11-35	NA	43-98	NA

NA, not applicable

The individual studies included in the review are summarized in Table 2. All four studies are randomized controlled trials and used the standard dose of 200 µg/kg ivermectin and 400 mg albendazole [4, 6-8]. Against infections with *T. trichiura*, CRs ranging from 27.5-81.1%, ERR based on geometric mean ranging from 91.3-99.7%, and ERR based on arithmetic mean ranging from 85.6-97.5% were observed. CRs for *T. trichiura* observed in Asian settings were higher than in African settings. One reason for this finding may be differences in the study design and quality (*e.g.* in terms of diagnostic approach used). Another possible reason recently highlighted is genetic diversity of *T. trichiura* strains and variation in susceptibility to anthelmintics and/or drug resistance [9-11]. Interestingly, the higher efficacy of ivermectin in combination with albendazole translated – at least in some settings – into lower prevalences even after one year [4, 12]. The efficacy of albendazole-ivermectin against *A. lumbricoides* was excellent (CRs >78% and ERRs >99.5%), while moderate CRs (50-66.7%) and high ERRs (>95.4%) were observed against hookworm.

Table 2. Known efficacy of co-administered ALB-IVM[a] against *T. trichiura*:

Study	**Setting**	**Cure rate in % (n_{neg}/n)**	**Eggs per gram (pre/post)**	**Egg reduction rate in %**
Ismail et al. 1999	Sri Lanka	81.1% (43/53)	1544.0/78.7 (unkwn)	94.9% (unkwn)
Belizario et al. 2003	Philippines	65.1% (97/149)	4948.1/122.5 (ar) 550.0/1.9 (geo)	97.5% (ar) 99.7% (geo)
Knopp et al. 2010	Tanzania (Pemba)	37.9% (53/140)	127/11 (geo)	91.3% (geo)
Speich et al. 2015	Tanzania (Pemba)	27.5% (30/109)	1059/153 (ar) 489/27 (geo)	85.6% (ar) 94.5% (geo)
All studies		**49.4% (223/451)**		

[a]*Considered doses: albendazole=400 mg, ivermectin=200 µg/kg*

ar=arithmetic mean, geo=geometric mean, unkwn=unknown mean

The WHO Expert Committee met from March 27-31, 2017 and, based on review of a dossier suggesting inclusion of ivermectin as an anthelmintic in the Essential Medicines List, made the following recommendation:

"…adding ivermectin on the Essential Medicines List under the section intestinal anthelminthic for use against Strongyloides stercoralis and STH. It may be used in combination with albendazole for treatment of soil-transmitted helminthiasis."

This important milestone paves the way for further, standardized trials to evaluate the efficacy of this combination among school-aged children in a range of epidemiological settings. In addition, the combination should be evaluated among adults, as there is growing interest in broadening deworming to include adults in order to move from morbidity control toward interruption of transmission [13, 14].

In the proposed work, three trials are planned across a range of transmission settings, including Côte d'Ivoire, Lao PDR, and Pemba (Tanzania). Follow-up will be conducted at 1, 6, and 12 months to inform treatment frequency. Results from these trials will inform decisions on how the combination could be introduced into

existing mass drug administration (MDA) programs and therefore provide a valuable adjunct tool for interrupting STH transmission.

3. Trial objective and purpose

The overall goal of the study is to assess the efficacy and safety of co-administered albendazole and ivermectin versus albendazole monotherapy (standard of care) against *T. trichiura* infections in children and adults (6-60 years) in different transmission settings and geographies.

We hypothesize that albendazole-ivermectin has a higher efficacy against *T. trichiura* infections than albendazole alone, and hence, the efficacy against all three STH species (*A. lumbricoides*, *T. trichiura*, and hookworm) and *Strongyloides stercoralis* will be increased.

The **primary objective** of the trial is to comparatively assess the efficacy in terms of CR against *T. trichiura* infections among school-aged children and adults from three different epidemiological settings and monitored over a 12-month period of the following two oral treatment regimens:

- Albendazole/ivermectin combination
- Albendazole monotherapy

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

a) To evaluate the safety and tolerability of the treatment regimens
b) To compare the ERRs of the treatment regimens against *T. trichiura*
c) To determine the CRs and ERRs of the drugs in study participants (6-60 years) infected with hookworm, *A. lumbricoides* and *S. stercoralis*
d) To investigate potential extended effects on follow-up helminth prevalences (6 and 12 months post-treatment) of the two treatment regimens (as assessed among participants with cleared infection on days 21 and 180)
e) To compare CRs based on infection status determined by novel polymerase chain reaction (PCR)-based and standard microscopic diagnosis
f) To assess potential differences in susceptibility to the treatment regimen between the three hookworm species, *Necator americanus, Ancylostoma duodenale* and *A. ceylanicum*, as classified through the novel PCR-based diagnosis
g) To characterize *T. trichiura* strains from different epidemiological settings and investigate potential resistance markers using a deep sequencing analysis
h) To determine optimal timing for measuring anthelmintic efficacy in *T. trichiura* infection
i) To evaluate potential benefits from deworming on morbidity (clinically evaluated and self-rated from questionnaire interviews) on microbiome and nutritional indicators

4. Methodology

4.1 Primary and secondary endpoint

T. trichiura infection status assessed by Kato-Katz 14-21 days after treatment will be the primary endpoint and the main outcome for efficacy be expressed as CR (*i.e.* conversion from being egg positive pre-treatment to egg negative post-treatment) and ERR (secondary end point). Secondary endpoints include further infection status with *A. lumbricoides*, hookworm and *S. stercoralis* and related efficacy measures, adverse events and infection status assessed by PCR. In addition, optimal timing for drug efficacy assessment in *T. trichiura* infection will be determined, *T. trichiura* strains and the microbiome will be described and potential resistance markers evaluated using deep sequencing and potential benefits on nutritional and morbidity indicators from treatment assessed (exploratory end points).

4.2 Type of trial

Double blind randomized controlled trial.

4.3 Trial design

4.3.1 Baseline survey and screening

A randomized-controlled trial will be conducted with two treatment arms to be followed-up over a 12 months period with an intermediate re-treatment of participants found re-infected after 6 months (Figure). This parallel group trial will be conducted as a multi-country study; thus, in each setting a separate trial according to the design described below will be set up, to provide a better basis for the subsequent generalization of its findings. This arises from the possibility of recruiting the subjects from a wider population and of administering the medication in a broader range of clinical settings, thus presenting an experimental situation that is more typical of future use. The study includes one baseline and three follow-up assessments at 3 weeks (day 21), 6 months (day 180), and 12 months (day 360).

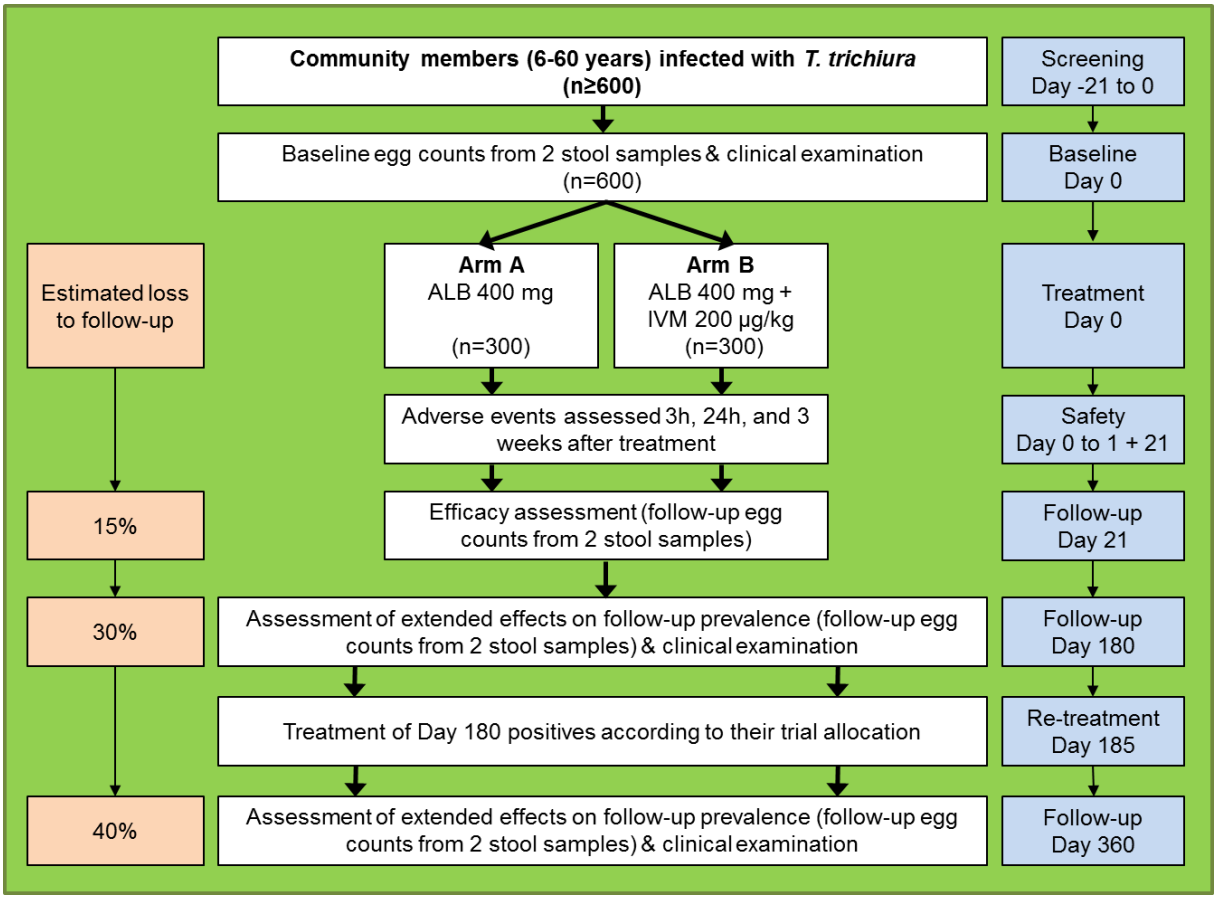

Figure 2. Design and timeline of the randomized-controlled trial to be implemented in each of three settings.

The study is designed as a two-armed trial including one arm with a single drug administration (arm A; albendazole) and one arm with combined treatment through co-administration of separate tablets (arm B; albendazole and ivermectin).

The trial will be conducted as a multi-country study with two settings in Africa and one in Asia, namely Côte d'Ivoire, Pemba (Zanzibar, Tanzania) and Lao PDR.

At baseline, all participants will be asked to provide two stool samples of at least 15 grams each (within a maximum of 5 days). From every stool specimen, duplicate Kato-Katz thick smears (41.7 mg each) [15] will be prepared and read under a microscope for eggs of *T. trichiura*, *A. lumbricoides* and hookworm by experienced technicians. A small amount of feces (~10 mg and 60µg, respectively) will further be tested on fecal occult blood and calprotectin as proxies for gut morbidity and inflammation using a rapid diagnostic test and an immunoassay, respectively [16]. Additionally, a portion of 1.5-2 g of stool from each specimen will be frozen and preserved in 70% ethanol, respectively and shipped to a reference laboratory at the Swiss Tropical and Public Health Institute (Swiss TPH, Basel, Switzerland) for microbiome and PCR analysis [17]. While discrimination of hookworm species via morphological comparison during microscopy of Kato-Katz slides is not feasible [18], PCR will allow to accurately determining efficacy and for further classification of hookworm infection into the three species *N. americanus, A. duodenale* and *A. ceylanicum*. The remains of each stool sample (ideally 10 to 20 g) will be processed by the Baermann technique for identification of *S. stercoralis* infections and be recorded qualitatively as larvae-positive or negative. ~~Urine samples from each participant will be collected together with the 2nd stool sample, fixed and transferred to a laboratory at Khon Kaen University in Thailand for subsequent detection of *S. stercoralis* antibodies using a novel ELISA-based assay.~~ At baseline and in the first follow-up (3 weeks post treatment) an additional portion of the second stool sample (1.5-2 g) from a

subsample of 10 participants identified with heavy intensity infections in each case (as assed on the first sample) will be preserved in 95% ethanol, shipped to the same reference laboratory at Swiss TPH in Switzerland and subjected to deep sequencing for characterization of *T. trichiura* strains and investigation of potential resistance markers [19]. A subsample of 30 participants in each treatment arm will be asked to provide a daily stool sample for a period of up to 4 weeks to monitor dynamics of *T. trichiura* egg output for subsequent determination of the optimal timing for drug efficacy assessment as has been done for other STH species earlier [20].

A subsequent independent quality control of sample results (approximately 10%) will be conducted. Results are considered correct if the following tolerance margin is not exceeded: (i) No difference in presence/absence of hookworm, *A. lumbricoides* and *T. trichiura*, (ii) egg counts are +/-10 eggs for counts ≤100 eggs or +/-20% for counts >100 eggs (for each species separately) [21]. 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 count per gram of stool (EPG) will be calculated for each treatment arm. All microscopically analyzed quadruplicate Kato-Katz thick smears will be destroyed within one day (after passing the quality control). The same sampling procedure and diagnostic approach will be applied at days 21, 180 and 360 post-treatment.

In the Asian setting potential complications through albendazole treatment in patients affected by (neuro-) cysticercosis due to infection with *Taenia solium* have to be considered and communities without pig-farming activities should be prioritized for study location selection [22].

A clinical examination of the study participants assessing general health, anthropometric parameters including height, weight, mid-upper arm circumference (MUAC) and skinfold thickness (i.e. triceps and subscapular skinfolds) as well as tympanic temperature using an ear thermometer will precede the treatment and will be repeated on two follow-up assessments (days 180 and 360) to evaluate potential benefits from deworming. Each participant will be asked to provide a finger-prick blood sample for a RDT for *Plasmodium* spp. infection and to evaluate hemoglobin (Hb) levels using a HemoCue analyzer (Hemocue Hb 301 system; Angelholm, Sweden) following the same (re-)assessment schedule. To assess potential improvement on nutritional indicators for micro- (*i.e.* (pro-) vitamins, inflammation markers, and iron/ferritin) and macronutrient (*i.e.* albumin) deficiencies and dynamics of biochemical blood parameters as a proxy for functioning of vital organs a venous blood sample (approximately 8 ml) will be taken at baseline, day 21, day 180 and 360. These samples will be analysed in Switzerland. The biochemical parameters to be assessed (in Laos) include urea, creatinine, bilirubin, azotemia, Alanine Amino Transferase (ALAT), Aspartate Amino Transferase (ASAT) as well as blood cell counts (*e.g.* hematocrit, erythrocytes and platelets). Refusal of patients to provide blood samples will be accepted. To avoid accidental treatment of pregnant girls/women all female participants (≥ 12 years) will be asked to provide a urine sample of at least 10 ml to be subjected to a pregnancy RDT on day 0 and day 180.

All trial participants will further be asked about existing clinical symptoms before drug administration. Additionally, they will be asked to provide subjective short-term (*e.g.* convenience of treatment) and long-term (*e.g.* effectiveness in reducing symptoms) treatment satisfaction embedded in the re-assessment questionnaires. As a measure of patient-rated physical functioning and wellbeing all children (6-16 years) will be administered a questionnaire before, 6 and 12 months after treatment, based and adapted from tools already validated in school-aged children from rural settings in Côte d'Ivoire [23]. Before application this tool will be adapted to local conditions of Lao PDR and pre-tested in a comparable school-aged population not otherwise involved in this trial. To adjust for known influencing factors with regard to reinfection and morbidity [24, 25] in the subsequent analysis and to identify risk factors for residual infections [26] a household-based questionnaire will be administered to one adult member of each participating household, assessing information on socioeconomic characteristics, access to sanitation and water facilities as well as hygiene behavior.

4.3.2 Assessment of efficacy and other benefits after treatment

The efficacy of the treatment will be determined 21 days post-treatment by collecting another two stool samples which will be microscopically examined for *T. trichiura* using duplicate Kato-Katz thick smears and potential

co-infection with *S. stercoralis* applying the Baermann technique ~~and the urine-based ELISA assay~~. Participants will be considered *T. trichiura* cured if no eggs have been found in the stool. EPG will be assessed by adding up the egg counts from the quadruplicate Kato-Katz thick smears and multiplying this number by a factor of six. Geometric and arithmetic mean egg counts will be calculated for the different treatment arms before and after treatment to assess the corresponding ERRs. The stool samples collected 21 days post-treatment for efficacy assessment will further be re-tested with the same rapid diagnostic test (including PCR and microbiome sampling) and immunoassay used at baseline to determine fecal occult blood and calprotectin levels. Frequencies of subjects found positive with either of the two markers and by intensity category for calprotectin will be calculated by treatment arm.
At the end of the study (approximately 12 months post-treatment) all participants remaining positive for *T. trichiura* and other soil-transmitted helminths will be treated with albendazole-ivermectin, the currently best approved and recommended treatment against *T. trichiura* [27].
Potential extended effects on follow-up helminth prevalences will be assessed using the same methodological approach as used for the efficacy assessment and will be based on stool samples collected 6 and 12 months post-treatment. Likewise fecal occult blood and calprotectin will be re-determined on the same stool samples.

To assess eventual reduction in morbidity and improvement in nutritional indicators all trial participants will be asked to provide another finger-prick blood sample at the 6 and 12 month follow-up for Hb measurement and rapid diagnostic testing (*i.e.* malaria) and once more a venous blood sample for micronutrient/blood parameter evaluation at all three follow-up time points, respectively. Anthropometric measurement including height, weight, MUAC and skinfold thickness will be repeated on the same occasion. Children (6-16 years) will be asked to re-assess their own physical functioning in repeated questionnaire interviews during these two last follow-ups. Long-term satisfaction with the treatment will be asked 6 months post-treatment. Mean values for continuous outcomes and frequencies for binary/categorical outcomes will be calculated for each treatment arm and follow-up time point and compared using descriptive and repeated measurement analysis as detailed in section 7.3.

4.4 Measure to minimize bias

Study participants eligible for treatment will be randomly assigned to one of the treatment arms using a computer-generated stratified block randomization code. The random allocation sequence with varying random blocks of four or eight and stratified by 2 levels of baseline infection intensity (light: <1000 EPG, and moderate plus heavy: ≥ 1000 EPG *T. trichiura* infections) will be provided by a statistician. The treatment arms will have an equal number of participants with light infection intensity, although the number of light versus moderate/heavy infections are not expected to be equal in each arm, depending on the distribution of infection intensity in the recruited cohort. The study will be double blinded (*i.e.* study participants and the trial team/researchers conducting the treatment and assessing the outcomes will be blinded) using repacked tablets including appearance-matched placebos.

4.5 Study duration and duration of subject participation

The trial will last fourteen months. The screening for the baseline will start three weeks prior to the treatment. Follow-up screening will take place 14-21 days, 180 days and 360 days post-treatment and last each time for about three weeks. Schedules of visits are summarized below.

4.6 Schedule of visits

Table 3. Schedule of visits of parallel group trial.

	Screening -21 to -1 days	**Baseline/Treatment/Safety** Hours 0		3	24	**Follow up** Days 21	180	185	360
Diagnosis (stool and urine examination)	X		**Randomization and treatment**			X	X	**Selective re-treatment**	X
Gut morbidity (stool RDTs)	X					X	X		X
Informed consent	X								
Demographics	X								
Medical history		X							
Clinical examination		X					X		X
Pregnancy testing		X					X		
Hemoglobin measurement		X					X		X
***Plasmodium* co-infection**		X					X		X
Venous blood examination		X				X	X		X
Physical functioning		X					X		X
Capturing AEs				X	X	X			
Capturing SAE				X	X	X			
Treatment satisfaction				X		X	X		

5. Selection of the trial subjects

5.1 Recruitment

The study will be carried out in community members aged 6–60 years in areas with moderate to high *T. trichiura* endemicity (communities with a prevalence ≥ 25%) identified from earlier studies and/or based on experience of the local collaborating teams. The trial will be implemented as community-based study in order to recruit participants from a broad age range (6–60 years). Ideally, entire communities with population size of < 1000 inhabitants will be included in the study for pre-screening and identification of *T. trichiura* cases to avoid potential selection bias of households. To identify all potentially eligible households of the respective communities and its composition in terms of age groups a preceding population census will be conducted.

All adult community members, including parents/caregivers of minor participants, will be invited to participate in an information meeting to explain the purpose and procedures of the study, including potential benefits and risks. Parents/caregivers/potential participants will be encouraged to ask questions in an open discussion forum. During this session, they will be informed of preventive actions they can take to help protect their children from

acquiring *T. trichiura* and other STH infections in the future (*e.g.* adequate food, preparation and defecation behavior).

Those parents/caregivers and their children 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. Written informed consent signed by either the participant him/herself (≥18 years of age) or by parents and/or caregivers for children/adolescents; and oral assent by child/adolescent (aged 6–17 years).
2. Agree to comply with study procedures, including provision of two stool samples at the beginning (baseline) and on three follow-up assessments (approximately 3 weeks, 6 months, and 12 months later).
3. Aged ≥6 to ≤60 years.
4. At least two slides of the quadruple Kato-Katz thick smears positive for *T. trichiura* and infection intensities of at least 100 EPG.

5.3 Exclusion criteria

1. No written informed consent by individual/parents and/or caregiver.
2. Below age 6 and 15 kg weight
3. Presence of major systemic illnesses, *e.g.* severe anemia (below 80 g/l Hb according to WHO [28]), clinical malaria as assessed by a medical doctor (positive *Plasmodium* RDT and ≥38 °C ear temperature), upon initial clinical assessment.
4. History of acute or severe chronic disease (*e.g.* cancer, diabetes, chronic heart, liver or renal disease).
5. Recent use of anthelmintic drug (within past 4 weeks).
6. Attending other clinical trials during the study.
7. Negative or low egg count (less than 100 EPG or less than 2 out of 4 slides positive) diagnostic result for *T. trichiura* eggs in the stool.
8. Known allergy to study medications (*i.e.* albendazole and ivermectin).
9. Pregnancy or lactating in the 1st week after birth (according to WHO guidelines within LF control programs [29]).
10. Currently taking medication with known interaction (*e.g.* for albendazole: cimetidine, praziquantel and dexamethasone; for ivermectin: warfarin).

5.4 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 a participant withdraws).

2. At the discretion of the Principal Investigator (PI) or co-PI, if the participant is not compliant to the requirements of the protocol.

Discontinued 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 (adverse events (AEs) monitoring) will be conducted.

5.5 Treatment of subjects

All *T. trichiura*-infected, consenting, and participating community members will be treated with the respective single or combination treatment regimen at day 0. 400 mg albendazole will be the product of Glaxo Smith Kline (Zentel®) and a single tablet administered. 3 mg tablets of ivermectin (Stromectol®) will be obtained from Merck, France, the weight recorded for each participant and the correct dose evaluated and administered. Matching ivermectin placebo tablets (in terms of appearance) will be produced and a certificate of manufacture and analysis be provided by the University of Basel. To ensure double-blinding the tablets will be repacked into neutral separate plastic bags each containing one albendazole tablet and the maximum number of ivermectin tablets with regard to weight and dose or the corresponding number of placebo tablets. Since albendazole and ivermectin are known to be better absorbed in humans after a high-fat meal was consumed, participants will receive a local high-fat breakfast (sandwich with *e.g.* oily sardines) prior to treatment [30, 31].

All drugs will be administered in the presence of the investigator(s), 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. The Principal Investigator 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.

Antimalarial treatment (*i.e.*, artemisinin-based combination therapy) will be provided to participants found with clinical malaria (*i.e.* positive *Plasmodium* RDT and ≥38 °C ear temperature) or severely anemic in combination with a positive RDT result. Iron supplementation will be offered to severely anemic individuals with a negative RDT result.

To avoid interference of potential on-going control programs against helminthiases with the infection status of the trial participants, communication with local stakeholders will be established to ascertain that trial participants will not undergo MDA treatment. Missed-out rounds of planned MDA against helminthiases in study participants will be substituted with a free single-dose treatment (*i.e.* albendazole 400 mg + ivermectin 200 µg/kg) against STH as well as *S. stercoralis* infection at the study endpoint (after the day 360 follow-up assessment) offered by the study team. At each follow-up time point, participants will be interviewed whether they had taken anthelmintic treatment (e.g. self-purchased, obtained from clinics etc).

5.6 Concomitant therapy

All medications taken one month before and during the study period until the last stool examination must be recorded with indication, dose regimen, date and time of administration.

Medication(s)/treatment(s) permitted during the trial:

- Analgesics and antipyretics are allowed to be given to the subjects in case of fever, antiemetics to prevent nausea and vomiting and/or antibiotics to prevent or treat bacterial superinfection.

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

- No other active drugs against helminths are permitted during the trial.

- No drugs with known interactions with the study medication are permitted during the trial.

6. Safety assessments

Few AEs have been reported following ivermectin-albendazole co-administration in STH-infected individuals. The most common AEs were abdominal cramps, headache, fatigue, nausea, diarrhea, fever and vertigo [7, 8, 32]. The safety profile of co-administered ivermectin and albendazole will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs and a physical and clinical examination.

6.1 Adverse event definitions

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

a) Any unfavorable and unintended signs, symptoms or disease temporally associated with the use of a medicinal product, whether or not considered related to the condition under study and the study product;

b) Any abnormality detected during physical examination.

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

The observation time for AEs starts when the treatment is initiated until day 21 (3 weeks after last drug administration).

These data will be recorded on the appropriate case report form (CRF) sections, regardless of whether they are thought to be associated with the study or the drug under investigation. Associated with the use of the drug means that there is a reasonable possibility that the event may have been caused by the drug (see also relatedness definitions below).

6.1.1 Severity grading

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

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

5 Death related to adverse events

6.1.2 Relatedness

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

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

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

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

6.1.3 Expectedness

Expected adverse drug reaction: Any AE possibly related to the co-administration of ivermectin-albendazole reported in the literature or on the drug package leaflets and listed in the consent form.

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

6.1.4 Serious adverse events

According to the ICH "Clinical Safety Data Management: Definitions and standards for expedited Reporting E2A" [33], a serious adverse event (SAE) includes any event (experience) or reaction in any untoward medical occurrence that at any dose:

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

A "severe" AE does not necessarily meet the criteria for a "serious" AE. SAEs are reported from consent to 3 weeks post-treatment (Day 21).

SAEs that are still ongoing at the end of the study period will be followed up to determine the final outcome.

The causality of any SAE that occurs after the study period and its possible relatedness to the study treatment or study participation will also be assessed by investigators as described in section 6.1.2.

6.1.5 Suspected unexpected serious adverse reactions

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

6.2 Methods of recording and assessing adverse events

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 and physical and biochemical 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 also be interviewed 3 and 24 hours and again 3 weeks after treatment about the occurrence of AEs (see chapter 4.6).

Information on all AEs (onset, duration, intensity, seriousness and causality) will be immediately entered in the appropriate AE module of the CRF that serves as 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 and iii) an assessment of intensity of AEs will be judged by the study physician.

All SAEs or SUSARs must be reported as described in Section 6.3.

6.3 Reporting of serious adverse events

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

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

6.4 Safety reporting to Health Authorities and 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 'Ethikkomission Nordwest- und Zentralschweiz' (EKNZ, Switzerland) and the ethics committee of Lao PDR according to national rules. Fatal or life-threatening SAEs or SUSARs will be reported within 24 hours followed by a complete report within 7 additional calendar days. Other SAEs and SUSARs that are not fatal or life-threatening will be filed as soon as possible but no later than 14 days after first knowledge by the sponsor.

7. Statistics

7.1 Definition of primary endpoint

CR of co-administered ivermectin-albendazole against *T. trichiura* is the primary endpoint in our study. Since treatment success is influenced by infection intensity, stratified block randomization will be used (baseline infection intensity: light infections and moderate/heavy infections) to ensure balanced treatment groups in terms of infection intensity.

7.2 Justification of number of trial subjects

Based on available summarized efficacy measures from a recent review [1] and the published literature, we assume that the CR of albendazole against *T. trichiura* is 30% compared to 50% in the albendazole-ivermectin treatment regimen. To detect a difference with 90% power at a two-sided 5% significance level, we require 121 participants per study arm and 143 to account for potential loss to follow-up of 15%. We further assume the same treatment efficacy in the mid-term treatment and a 6-months reinfection risk of 10%. Consequently we expect a proportion of negative patients after 12 months of 44% in the albendazole arm and of 65% in the albendazole-ivermectin arm resulting in a required sample size of 111 participants per arm. To account for a loss to follow-up of 30% after 6 months and 40% at final assessment (12 months) we aim to recruit 300 participants in each treatment group (600 in total) in each country.

Subgroup analysis will be conducted stratifying the study population by age category (school-aged and adults). For the subgroup analysis we will pool the data from all 3 countries to ensure sufficient statistical power.

7.3 Description of statistical methods

The primary available case analysis will include all participants with primary end point data. In addition, an intention-to-treat analysis will be conducted considering all participants with missing endpoint data as treatment failure or all as treatment success to ensure that the results are not sensitive to potential loss to follow-up bias. CRs will be calculated as the percentage of egg-positive (larvae-positive for *S. stercoralis*) children at baseline who become egg-negative (larvae-negative) after treatment. EPG will be assessed by adding up the egg counts from the quadruplicate Kato-Katz thick smears and multiplying this number by a factor of six. For *S. stercoralis* infection no further quantification of larvae in stool will be done. The ERR of STH infection will be calculated as:

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

In the primary model we estimate the difference among CRs by using unadjusted logistic regressions. In a subsequent analysis an adjusted logistic regression (adjustment for age, sex, and weight) will be performed.

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

Results from the stool RDT for fecal occult blood will be categorized as negative, trace and positive. For calprotectin, individuals with levels exceeding 50 µg/g will be considered as positive and concentrations be classified into low (51–149 µg/g), medium (150–299 µg/g) and high (≥300 µg/g) intensity [16].

Anthropometric measurements such as height and weight of school-aged children will be translated into weight- and height-related z-scores using readily available Stata macros calculating growth indicators for children 5-19 years [34]. Body mass index and indicators for muscle and fat tissue such as MUAC and skinfold thickness will serve as additional indicators of nutritional status for adults and will further be classified using a percentiles approach to compare within populations [35].

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 [23].

Nutritional and morbidity indicators will be analysed using logistic and linear regression as appropriate. To compare individual's changes in nutrition/morbidity categories as an effect from treatment McNemar's test will be applied. The analysis after 6 and 12 month of follow-up will be complemented by generalized estimating equation (GEE) models with independent correlation structure and empirical estimators to account for missing data.

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

7.4 Description of data management and data quality control

The investigators are responsible for an adequate data quality. Prior to the initiation of the study, a short investigator's meeting will be held with the investigators and their study coordinators and a member from Swiss

TPH. This meeting will include a detailed discussion of the protocol, performance of study procedures (standard operating procedures (SOPs) from previous studies available on site), CRF completion, and specimen collection and diagnostic methods.

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

1. Eggs counts of *T. trichiura*, *A. lumbricoides* and hookworm and infection status with *S. stercoralis* based on participants' stool samples analyzed using the Kato-Katz and Baermann technique, respectively, before (baseline) and at 3 time points after treatment (follow-ups after 3 weeks, 6 and 12 months). Presence of fecal occult blood and elevated calprotectin levels will be evaluated and recorded applying RDTs on the same stool samples and assessment time points.
2. Personal information such as name, age, gender and household composition of trial participants.
3. Anthropometric and clinical characteristics of the trial participants collected using the study's CRF such as weight, height, skinfold thickness, blood pressure, temperature, hemoglobin level, infection status with *Plasmodium spp*., any abnormal medical condition or chronic disease as well as pregnancy in female participants 10 years and above.
4. Number and type of AEs registered in the CRF actively probed for 3 and 24 hours after treatment. The same data will be collected during the collection of the first sample at the 3-week follow-up.
5. Scales for participant-rated treatment satisfaction and self-rated physical functioning in school-aged children captured on different time points (i.e. 3 weeks and 6 months and baseline, 6 and 12 months after treatment, respectively) and recorded on the CRF.
6. Concentration levels of blood and biochemical parameters together with indicators for micronutrient status as well as presence of *S.stercoralis* antibodies in urine before (baseline) and at 3 time points after treatment (follow-ups after 3 weeks, 6 and 12 months).
7. Household-level data on socioeconomic characteristics, presence and use of water and sanitation as well as hygiene-related attitudes and practices.

All data on parasitology and questionnaires about AEs, self-reported clinical signs and symptoms, physical functioning, and treatment satisfaction (data in category 1 to 5) will be paper-captured and subsequently entered (data entry SOP) into tablets using Open Data Kit (ODK; free electronic data collection software) and uploaded to a server hosted at Swiss TPH by trained team members. For quality assurance in-built error, range and consistency checks will be programmed for the ODK data entry masks. Data in category 6 will be provided in a paper or electronic format, as appropriate, by the respective external laboratories examining these parameters, and be subjected to double entry into ACCESS data entry masks by two independent persons; all double-entered data will be cross-checked using the Data Compare utility of EpiInfo. Any discrepancies identified from programmed quality checks or from comparing double entries will be corrected by consulting the hard copy. Data in category 7 will be directly entered while collecting into tablets using ODK and subsequently uploaded to the server at Swiss TPH. All categories will be merged into a single master file saved in .dta, .xlsx and .csv. Data will then be analysed as described in section 7.3. Hard copies of the data collected within the trial country such as parasitological, stool RDT, blood parameter sheets and CRFs will remain at Lao Tropical and Public Health Institute (Lao TPHI). 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 Lao TPHI. All data is expected to not exceed 5GB.

Invited and screened patients will be listed in a confidential "subject identification list and 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 pseudonymised data and will only be accessible to the local principal investigator. All study-specific data will only contain this unique identifier instead of any names. All data that have been hand-entered in the ACCESS database will be verified by a double-key entry procedure in a validated electronic data base system and error, range and consistency checks will be programmed. Any discrepancies will be reviewed against the hard copy CRF and corrected. Electronic data files will be stored on secured network drives with restricted access for study personnel only. Data analysis will be conducted with pseudonymised data and reporting of findings will be fully anonymised. All databases will be password secured.

Essential infrastructure such as lockable cabinets for safe storage of hardcopy data will be made available. Network drives with restricted access for authorized personnel only and appropriate analysis software are available.

8. Duties of the investigator

8.1 Investigator's confirmation

This trial will be conducted in accordance with the protocol, International Conference on Harmonization Good Clinical Practice E6 (R2) (ICH-GCP) and the current version of the Helsinki Declaration.

All protocol modifications must be documented in writing. A protocol amendment can be initiated by either the Sponsor/PI or any Investigator. The Investigator will provide the reasons for the proposed amendment in writing and will discuss with the Sponsor/PI and Co-PIs. Any protocol amendment must be approved and signed by the Sponsor/PI and must be submitted to the appropriate Independent Ethics Committee (IEC) for information and approval, in accordance with local requirements, and to regulatory agencies if required. Approval by IEC must be received before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial 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) and patient liability insurances will be issued in the respective trial countries.

8.3 Project management

The trial team will include the PI (Prof. Jennifer Keiser), two Co-PIs (Dr. Eveline Hürlimann and Dr. Somphou Sayasone) whereof the latest also acts as a study physician, a trial statistician (Dr. Jan Hattendorf), nurses and laboratory technicians. Prof. Jennifer Keiser, Dr. Eveline Hürlimann and a PhD student will be responsible for staff management, communication with the collaborative group, recruitment monitoring, data management, safety reporting, analysis, report writing and dissemination of the trial results. Dr. Somphou Sayasone and the PhD student will monitor all field activities at the study site.

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

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

9.2 Evaluation of the risk-benefit ratio

Ivermectin in combination with albendazole are well-known, widely used drugs in mass treatment programs against filariasis, and have little and mainly mild AEs (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 *T. trichiura* will be treated with ~~ivermectin (200 µg/kg)~~-albendazole (400 mg) ~~considering higher efficacy compared to the existing standard treatment (albendazole monotherapy) and recent inclusion as recommended treatment scheme on the Essentials Medicines List [27]~~ following national 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 parents or caregivers of eligible children and all adult participants (≥18 years) will be individually informed about benefits and risk associated to the trial. They will have sufficient time for reflection of their child's or their own participation, respectively. 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. In addition to a written informed consent form signed by their parent or caregiver, minor participants (aged 6-17 years) will also be briefed verbally and asked orally for assent. Even if the minor participant gives written assent, the parent/caregiver has to sign the consent.

Information sheets are printed in English but will additionally be verbally translated into local languages (*i.e.* Lao) during community meetings. To all participants and parents/caregivers 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.

Patients will be informed in case irregularities are observed on their health status during clinical examination and the assessment of biochemical blood parameters and if necessary referred to a health care center.

9.4 Subject confidentiality

The obtained data will be handled strictly confidentially. Only members of the study team will have access to the data. Personal data will be coded for data analysis. The codes will be filled with the participant's identity on a separate file (subject identification list and screening log) and stored in a secured place at the local institutions

(*i.e.* Côte d'Ivoire: Centre Suisse de Recherches Scientifiques en Côte d'Ivoire (CSRS), Lao PDR: Lao TPHI, and Pemba: Public Health Laboratory Ivo de Carneri) and will only be accessible to investigators. 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.

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 include school-aged children, since *T. trichiura* infection occurs often in children; hence this age group is at high risk of infection and is therefore the major target group in MDA campaigns. Our trial will produce more evidence to support the search for a safe and effective treatment scheme against STH infections in children and whole communities.

10. Quality control and quality assurance

10.1 Monitoring and auditing

We will work with locally based monitors. These will conduct site visits to the investigational facilities for the purpose of monitoring the study. Details will be described in a separate monitoring plan. The investigator will permit them access to study documentation and the clinical supplies dispensing and storage area. Monitoring observations and findings will be documented and communicated to appropriate study personnel and management. A corrective and preventative action plan will be requested and documented in response to any audit observations. No sponsor initiated audits are foreseen, but audits and inspections may be conducted by the local regulatory authorities or ethics committees. The Investigator agrees to allow inspectors from regulatory agencies to review records and is encouraged to assist the inspectors in their duties, if requested.

10.2 Access to data, handling of data and samples (data protection), archiving (place, duration) and destruction

Information about study subjects will be kept confidential and managed accordingly. A paper 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.

All data on parasitology and questionnaires about AEs, self-reported clinical signs and symptoms, physical functioning, treatment satisfaction and household-based socioeconomic factors and access to water and sanitation will be doubled entered into a database by two independent persons and cross-checked. Discrepancies between data entries will be corrected by consulting the hard copy.

The results of the research study will be published, but subjects' names or identities will not be revealed. Records will remain confidential. To maintain confidentiality, the Sponsor-Investigator will keep records in locked cabinets and the results of tests will be coded to prevent association with participant's names. Data entered into the ACCESS data entry mask will be accessible only by authorized personnel directly involved with

the study and will be encoded. Subject-specific information may be provided to other appropriate medical personnel only with the subject's permission for adults or the parent/caregiver's permission for minors.

After the study has been completed all samples will be destroyed and research data and related material will be kept 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. Storage and backup will be in three places: personal laptops of Jennifer Keiser, Eveline Hürlimann, and Somphou Sayasone, Swiss TPH shared server and SWITCHdrive (a cloud storage supported by University of Basel). Archiving conditions will be made strictly confidential by password protection.

10.3 Data entered directly in the CRF – definition of source data

Source Data are the clinical findings and observations, laboratory data maintained at the study site. Source data are contained in **source documents**. Local authorities are allowed to access the source data. Data will be entered directly onto the CRFs. The CRF is considered as a source document. All CRFs will be kept for at least 15 years.

The study site will retain the original 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.

10.4 Data and safety monitoring board/ data monitoring committee

In our study no data and safety monitoring board will be established, since we work with well-known drugs in a limited number of participants and using a single dose treatment. This study is anticipated to be no greater than minimal risk to participants.

10.5 Study Documents: Translations - Reference language

- 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.

11. Dissemination of results and publication

The final results of this study will be published in a scientific journal and presented at scientific conferences. The Bill & Melinda Gates Foundation will be acknowledged as study funder. All results from this investigation are considered confidential and shall not be made available to any third party by any member of the investigating team before publication. A summary of study conclusions will be shared with the local ethics committees and the national regulatory authorities.

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7. Statistical Analysis Plan (SAP)

Clinical trial protocol title:	Efficacy and safety of ivermectin and albendazole co-administration in school-aged children and adults infected with *Trichuris trichiura*: a multi-country randomized controlled trial
Principal Investigator	Jennifer Keiser
ClinicalTrials.gov identifier	03527732
Author	Jan Hattendorf
Version/Date	v1.0/14.9.2020

Contents

Signatures

The following persons have read and agreed on the SAP:

Jan Hattendorf

Trial Statistician

Date of signature 14.9.2020

Jennifer Keiser

Principal investigator

Date of signature 14.9.2020

Introduction

This Statistical Analysis Plan (SAP) is based on the current trial protocols versions v1.01_19.09.2018 (Lao PDR), v1.03_22.11.2018 (Côte d'Ivoire) and v1.01_13.2.18_(Zanzibar).

Where statistical methods differ substantially between this SAP and the protocol, the differences will be identified in the SAP.

This SAP describes the datasets and the statistical methods to be used for the reporting and analysis of all data collected 3 weeks after treatment in **three randomized controlled trials**. If a future protocol amendment necessitates a substantial change to the statistical analysis of the trial data, this SAP will be amended accordingly.

If, after database lock, deviations or additional analyses are required to supplement the planned analyses described in this SAP, those will not be described in an amended SAP, but they will be identified in the related publication.

This SAP has been written in consideration of the following guidelines:

- International Conference on Harmonization (ICH) E9, Guidance for Industry: Statistical Principles for Clinical Trials (ICH E9 1998)1
- ICH E3, Guidance for Industry: Structure and Content of Clinical Study Reports (ICH E3 1995)

Statistical analysis will be done using R 5.3.1 on a Windows 64 bit system.

Study Objectives and Endpoints

Study Objectives

Primary Objective

To assess the efficacy and safety of standard doses of co-administered ivermectin (200 µg/kg) and albendazole (400 mg) against *Trichuris trichiura* compared to albendazole (400 mg) alone in community members aged 6-60 years.

Secondary Objectives

To evaluate the safety and tolerability of the treatment regimens

To compare the egg reduction rate (ERR) of the treatment regimens against *T. trichiura*

To determine the CRs and ERRs of the drugs in study participants (6-60 years) infected with hookworm, *Ascaris lumbrico*ides and *Strongyloides stercoralis*

Study Endpoints

Primary

T. trichiura cure rate (CR) defined as infection status assessed by Kato-Katz 14-21 days after treatment expressed as cure rate, i.e. conversion from being egg positive pre-treatment to egg negative post-treatment.

Secondary

ERR against *T. trichiura*

CRs and ERRs against *A. lumbricoides*, hookworm and *S. stercoralis*

Adverse events

Infection status assessed by PCR

Safety

Statistical Hypotheses

Primary hypothesis: albendazole-ivermectin has a higher efficacy against *T. trichiura* infections compared to albendazole alone.

Study Design

This is a multi-center, blinded, randomised, SoC-controlled, parallel-group, single-dose, superiority trial. Participants in the albendazole monotherapy arm will receive a matching ivermectin placebo. Double blinded (study participants, trial team/researchers conducting the treatment and outcome assessors) using repacked tablets including appearance-matched placebos. Computer-generated stratified block randomization code. The random allocation sequence with varying random blocks of four or eight and stratified by 2 levels of baseline infection intensity. Tablets together with the respective treatment arm label were pre-packed by researchers not involved in this trial into small opaque envelopes labelled with the unique IDs to ensure allocation concealment.

Time and Events Table

	Screening	**Baseline/Treatment/Safety**				**Follow up**			
	Days	Hours				Days			
	-21 to -1 days	0		3	24	21	180[a]	185[a]	360[a]
Diagnosis (stool and urine examination)	X		**Randomization and treatment**			X	X	**Selective re-treatment**	X
Gut morbidity (stool RDTs)	X					X	X		X
Informed consent	X								
Demographics	X								
Medical history		X							
Clinical examination		X					X		X
Pregnancy testing		X					X		
Hemoglobin measurement		X					X		X
***Plasmodium* co-infection**		X					X		X
Venous blood examination		X				X	X		X
Physical functioning		X					X		X
Capturing AEs				X	X	X			
Capturing SAE				X	X	X			
Treatment satisfaction				X		X	X		

[a] not subject of this SAP

Planned Analyses

Interim Analyses

Because of the short follow-up period, no interim analyses are planned.

Final Analysis

The database will be locked after all subjects have completed the study and the data have been entered, validated and all queries are resolved.

Sample size consideration

Each of the three trials was powered to detect a difference with 90% power at a two-sided 5% significance level assuming a CR of albendazole against *T. trichiura* is 30% and 50% in the albendazole-ivermectin treatment regimen. We anticipate to enrol 143 participants per study arm (including a potential loss to follow-up of 15%). For sub group analysis the data from all trials will be pooled to ensure sufficient power. Further details on the justification of study subjects are provided in the trial protocols.

Populations for analysis

Available case population: All participants randomized, excl. those who entered the study even though they did not satisfy the entry criterion 'positive at baseline' with at least one non-missing endpoint data.

Per protocol population: All participants who meet all inclusion and exclusion criteria, have no major protocol deviations and received the correct treatment.

Intention to treat population: All participants randomized, excl. those who entered the study even though they did not satisfy the entry criterion 'positive at baseline'

Safety population: All subjects who received at least one dose of treatment with at least one non-missing safety endpoint with no major protocol deviations.

Efficacy endpoints will be analysed using the available case population according to the ITT principles. The primary analysis will be confirmed using the per-protocol population. Safety endpoints will be analysed using the safety population as treated.

Subgroup analyses

The following pre-specified sub group analyses will be conducted:

- by age category (6-12 years vs. 13+ years)
- by baseline infection intensity (light vs moderate & heavy)

For sub group analyses the data from all trials will be pooled to ensure sufficient power.

Data handling conventions and missing data

All subjects who withdraw prematurely from the study or study drug will be included in the statistical analyses. Experience from previous trials indicated that the proportion of missing data is usually below 10%; therefore, no imputation of missing data is planned. In case the proportion of missing data will be considerably higher than expected the primary analysis using the available case population will be complemented by an analysis using the

intention-to-treat population. For this purpose missing data will be imputed by multiple imputations as implemented in R's 'mi' package.

Protocol deviations

Before closing the database, data listings will be reviewed to identify any significant deviations and determine whether the data should be excluded from any analysis populations.

Protocol deviations leading to exclusion from all analyses populations

- Participants who were negative for *T. trichuria* infection at baseline.

Major protocol deviations include subjects who:

- Entered the study even though they did not satisfy other entry criteria.
- Met the criteria for withdrawal from the study but were not withdrawn.
- Received no treatment, the wrong treatment or incorrect dose.
- Received an excluded concomitant therapy.

Minor protocol deviations include subjects who:

- Provided fewer stool samples than specified in the protocol
- Provided stool samples later than specified in the protocol (measurements taken outside the allowable windows given in the protocol)
- Vomiting within 1-hour post-dosing without re-treatment.

Participants with major protocol deviations will be excluded from the per-protocol population. Minor protocol deviations will remain in all analysis populations.

Demographics and other baseline characteristics

Baseline characteristics will be calculated and presented as outlined below

Characteristics	Pemba Island		Côte d'Ivoire		Lao PDR	
	ALB (n=xxx)	**IVM-ALB (n=xxx)**	**ALB (n=xxx)**	**IVM-ALB (n=xxx)**	**ALB (n=xxx)**	**IVM-ALB (n=xxx)**
Age, 6-12						
Age, 13-24yrs						
Age, 25 years and above						
Sex, n (%)						
Females						
Males						
Weight, kg						
Height, cm						
T. trichiura infection						
Geometric mean EPG						
Infection intensity[a], n (%)						
Light						
Moderate						
Heavy						
A. lumbricoides infection						
Infected, n (%)						
Geometric mean EPG						
Infection intensity[b], n (%)						
Light						
Moderate						
Heavy						
Hookworm infection						
Infected, no. (%)						
Geometric mean EPG						
Infection intensity[c], n (%)						
Light						
Moderate						
Heavy						
S. stercoralis infection[d]						
Infected, n (%)						

[a] *T. trichiura* infection intensity classified according to mean eggs per gram of stool (EPG) into: light=1-999 EPG, moderate=1000-9999 EPG and heavy=≥10000 EPG

[b] *A. lumbricoides* infection intensity classified according to mean eggs per gram of stool (EPG) into: light=1-4999 EPG, moderate=5000-49999 EPG and heavy=≥50000 EPG

[c] Hookworm infection intensity classified according to mean eggs per gram of stool (EPG) into: light=1-1999 EPG, moderate=2000-3999 EPG and heavy=≥4000 EPG

[d] Baermann technique to detect *S. stercoralis* infection was only applied to stool samples collected in Lao PDR

Efficacy analysis

In the unadjusted analysis the differences in cure rates will be assessed using a Melded Binomial Confidence Intervals and Tests with mid-p correction as implemented in the 'exact2x2' package.

```
library(exact2x2)
binomMeld.test( ... ,   # insert n[pos] and n[total]
   parmtype = "difference", conf.level = 0.95, conf.int = TRUE,
   alternative = "two.sided", midp = T)
```

This analysis has been chosen because most biomedical journals prefer the absolute difference over the relative difference. However, adjustment for confounder or effect modifier is not possible; therefore, the adjusted analysis will use standard logistic regression.

Egg reduction rates (geometric mean based) will be calculated using the following formula

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

Differences in geometric mean based ERR will be analysed via bootstrap resampling using the following code

```
# 1st column in data 'd' = baseline, 2nd = follow-up, arm = 'arm'
# Egg reduction rates geometric mean
ERRgm <- function(d, i) {
        return(1-(exp(sum(log(d[i ,2]+1))/length(d[i ,2]))-1)/
                (exp(sum(log(d[i ,1]+1))/length(d[i ,1]))-1))
}

# Difference Egg reduction rates geometric mean
diffgm <- function(d,i) {
        d <- d[i,]
        gmbl <- tapply(X=d[,1], INDEX=d$arm, gm)
        gmfu <- tapply(X=d[,2], INDEX=d$arm, gm)
        Diff <- (1-(gmfu[1]/gmbl[1])) - (1-(gmfu[2]/gmbl[2]))
        return(Diff)
}

library(boot)
difgm <- boot(data = d, statistic = diffgm, R = 2000, strata = d$arm)
```

The arithmetic based ERR will be estimated in the same way.

If the sample size of study participants infected with hookworm, Ascaris lumbricoides and *Strongyloides stercoralis* is considered sufficiently large, efficacy against these parasites will be assessed in the same way. If the number of participants will be below 100 per arm the trial arms will only be compared descriptively.

Efficacy results and estimates will be presented as outlined below

		Pemba Island		**Côte d'Ivoire**		**Lao PDR**		**Total**	
Variable		**ALB (n=xxx)**	**IVM-ALB (n=xxx)**	**ALB (n=xxx)**	**IVM-ALB (n=xxx)**	**ALB (n=xxx)**	**IVM-ALB (n=xxx)**	**ALB (n=xxx)**	**IVM-ALB (n=xxx)**
T. trichiura									
No. of participants positive for infection									
	Before treatment								
	After treatment								
Cure rate, % (95% CI)									
No. of participants cured n (%)									
	From light infection								
	From moderate infection								
	From heavy infection								
Geometric mean EPG									
	Before treatment								
	After treatment								
GM Egg-reduction rate, % (95% CI)									
Arithmetic mean EPG									
	Before treatment								
	After treatment								
AM Egg-reduction rate, % (95% CI)									
A. lumbricoides									
N participants positive									
	Before treatment								
	After treatment								
Cure rate, %									
N participants cured (%)									
	From light infection								
	From moderate infection								
	From heavy infection								
Geometric mean EPG									
	Before treatment								
	After treatment								
Egg-reduction rate, %									
Hookworm									
N participants positive									

	Before treatment								
	After treatment								
Cure rate, %									
N participants cured (%)									
	From light infection								
	From moderate infection								
	From heavy infection								
Geometric mean EPG									
	Before treatment								
	After treatment								
Egg-reduction rate, %									
***S. stercoralis*[a]**									
No. of participants positive for infection									
	Before treatment								
	After treatment								
Cure rate, %									

EPG: eggs per gram of stool

[a] *S. stercoralis* infection was assessed qualitatively only (positive vs negative) in stool samples collected in Lao PDR

Safety analysis

Adverse events will be analysed descriptively and summarized (for each country) as outlined in the 2 tables below.

Table: Adverse events assessed at baseline, 3 hours and 24 hours post treatment by treatment arm

	Before treatment	**3h post treatment**	**24h post treatment**	**After 24h**
ALB				
Total participants assessed				
Participants with AE				
% participants with AE				
Number of AEs				
IVM-ALB				
Total participants assessed				
Participants with AE				
% participants with AE				
Number of AEs				
TOTAL				
Total participants assessed				
Participants with AE				
% participants with AE				
Number of AEs				

	Baseline						**3h post-treatment**						**24h post-treatment**					
	ALB		**IVM-ALB**		**TOTAL**		**ALB**		**IVM-ALB**		**TOTAL**		**ALB**		**IVM-ALB**		**TOTAL**	
Adverse event	N, Any grade	N, Grade ≥2	N, Any grade	N, Grade ≥2	N, Any grade	N, Grade ≥2	N, Any grade	N, Grade ≥2	N, Any grade	N, Grade ≥2	N, Any grade	N, Grade ≥2	N, Any grade	N, Grade ≥2	N, Any grade	N, Grade ≥2	N, Any grade	N, Grade ≥2
Headache																		
Abdominal pain																		
Itching																		
Nausea																		
Vomiting																		
Diarrhea																		
Fever																		
Allergic reaction																		
Other																		

Table: Specific adverse events by treatment arm and time point