# An Adaptive phase II/III Single-Blinded, Randomized, Multi-Centre, Parallel-Group, Active-Controlled, Superiority Study to Evaluate the Safety and Efficacy of a Single Day or 3-day Single Dose of an ALBENDAZOLE-IVERMECTIN Co-formulation vs ALBENDAZOLE for the Treatment of Soil-Transmitted Helminth Infections (*Trichuris trichiura*, hookworm, *Strongyloides stercoralis*) in Paediatric and Young Adult Population (ALIVE Study)

**Short title: Evaluation of the effectiveness of ALBENDAZOL-IVERMECTIN co-formulation vs ALBENDAZOLE for the treatment of intestinal worms**


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## STATEMENT OF COMPLIANCE

I have read this protocol and agree that it contains all the necessary details for its conduct and execution. I agree to abide by all the provisions set forth therein. I agree to comply with the principle of the International Conference on Harmonisation Good Clinical Practice (ICH E6(R2)) and all applicable regulatory requirements regarding the obligations of clinical investigators.

The protocol, informed consent form(s) and all participant materials will be submitted to the relevant IRB or EC for review and approval. Approval of the protocol and the consent and assent forms will be obtained before any participant is recruited. Changes to the protocol or consent or assent forms will be submitted for review and approval by the IRB/EC or Regulatory authorities before the changes are implemented to the study.

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|---|---|---|
| Jose Muñoz, MD MSc PhD<br>Principal Investigator Name | Investigator Signature | Date |
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**Confidentiality Statement**

This document in its entirety contains confidential information that must not be disclosed to anyone other than the trial Sponsor, the Investigators, the Data Safety and Management Board and Scientific Technical and Advisory Board, IRB/EC or Regulatory authorities. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Principle and Chief Investigators.

# 1 PROTOCOL SUMMARY

## 1.1 SYNOPSIS

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| **Title:** | An Adaptive phase II/III, Single-Blinded, Randomized, Multi-Centre, Parallel-Group, Active-Controlled, Superiority Study to Evaluate the Safety and Efficacy of a Single Day or 3-day Single Dose of an ALBENDAZOLE-IVERMECTIN Co-formulation vs ALBENDAZOLE for the Treatment of Soil-Transmitted Helminth Infections (*Trichuris trichiura*, hookworm, *Strongyloides stercoralis*) in Paediatric and Young Adult Population. |
| **Phase** | II/III |
| **Study Description:** | An adaptive phase II/III clinical trial to evaluate the Safety and Efficacy of a Single Day or 3-day Single Dose of an ALBENDAZOLE-IVERMECTIN Co-formulation vs ALBENDAZOLE for the Treatment of Soil-Transmitted Helminth Infections.<br>The estimated total sample size for the adaptive design (phase II and III components) is 1223 participants. Of these, 126 will be enrolled in the phase II and 1097 in the phase III components .<br><br><u>Phase II component (Kenya only)</u><br>Unicentric, 3-arm, parallel, open-label, individually randomised, phase II trial to determine in three weight groups, the **safety** of the ALBENDAZOLE-IVERMECTIN Co-formulation given as a Single Day or 3-day Single Dose regimen for the treatment of *Trichuris trichiura* in children and young adult aged between 5 to 18 years.<br>**Estimated sample size:** 126 participants<br>Participants will be stratified in three different weight groups in order to gradually increase the dose of ivermectin in the Fixed Dose Co-formulation (FDC):<br>• Group 1 (38 participants): with body weight of 23-<30 Kg will receive 300-391 µg/Kg IVM (FDC 400mg-9mg) or ALB. |

- Group 2 (38 participants): with body weight of 30-45 Kg will receive 400-600 µg/Kg IVM (FDC 400mg-18mg) or ALB.
- Group 3 (50 participants): with body weight of 15-23 Kg will receive 391-600 µg/Kg IVM (FDC 400mg-9mg) or ALB.

Where FDC stands for Fixed Dose Co-formulation and ALB stands for Albendazole.

| Weight (Kg) | Study drug | Equivalent ivermectin dose received (µg/Kg) |
|---|---|---|
| 15 | FDC 400mg ALB-9mg IVM | 600 |
| 23 | FDC 400mg ALB-9mg IVM | 391 |
| 30 | FDC 400mg ALB-9mg IVM | 300 |
| 30 | FDC 400mg ALB-18mg IVM | 600 |
| 45 | FDC 400mg ALB-18mg IVM | 400 |

Then, the participants will be allocated to one of the three study arms with unequal probability (ALB: p=0.2, n=26; FDCx1: p=0.4, n=50; FDCx3: p=0.4, n=50) starting with group 1.

**Treatment Arm 1:** Single dose of a tablet of ALBENDAZOLE 400 mg (active control arm).

**Treatment Arm 2**: Single dose of a tablet of ALBENDAZOLE-IVERMECTIN Co-formulation.

**Treatment Arm 3:** Daily dose of a tablet of ALBENDAZOLE-IVERMECTIN Co-formulation for 3 consecutive days.

<u>Phase III Component</u>

A multi-centre, 3-arm, parallel, open-label, randomised, phase III trial to compare **safety and efficacy** of the active control arm (current standard of care) against 2 experimental arms for the treatment of *T. trichiura*, hookworm and *S. stercoralis*, in children and young adult aged between 5-18 years in three sub-Saharan African countries (Ethiopia, Kenya and Mozambique).

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| | We hypothesise that the FDC of Ivermectin (IVM) and ALB either at single or 3-day regimens will be more effective against some species of Soil Transmitted Helminths (STH) (*T. trichiura,* hookworm and *S. stercoralis*) compared to the current use of a single dose regimen of 400mg ALB.<br>**Estimated sample size:** 1097 participants<br>Participants will be randomly allocated with unequal probability, according to the specific expected cure rate by treatment and specie, to one of the three study treatment arms:<br>**Treatment Arm 1:** Single dose of a tablet of ALB 400 mg (active control arm).<br>**Treatment Arm 2:** Single dose of a tablet of FDC 400mg-18mg or 400mg-9mg.<br>o For participants <45 kg of body weight at baseline: FDC of 400mg ALB- 9mg IVM.<br>o For participants ≥45 kg of body weight at baseline: FDC of 400mg ALB-18mg IVM.<br>**Treatment Arm 3:** Daily dose of a tablet of FDC 400mg-18mg or 400mg-9mg for 3 days.<br>o For participants <45 kg of body weight at baseline: FDC of 400mg ALB-9mg IVM.<br>o For participants ≥45 kg of body weight at baseline: FDC of 400mg ALB- 18mg IVM.<br>In the phase III component, allocation of participants to study arms will be done by block randomization and stratified by the species of STH. Treatment allocation for each study participant will be concealed in opaque sealed envelope that will be opened only after enrolment. Study participants will be assigned a unique number linked to the allocated treatment group. |

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| | The phase II and III trial components comprise of a screening phase, an enrolment phase, a treatment phase, a post-treatment phase with follow-up visits, and early withdrawal/end-of-study evaluations.<br>Participants recruited in Mozambique will be offered to be tested for HIV serostatus due to the high HIV prevalence in the country, but the result will not determine the participant's eligibility. In Kenya and Ethiopia, the low HIV prevalence does not justify HIV testing. |
| **Objectives:** | **<u>Phase II component</u>**<br>**Primary Objective:**<br>1. To evaluate the **safety** of the FDC as a single dose or 3-day single dose regimen for the treatment of *T. trichiura* in paediatric population.<br>**Secondary Objectives:**<br>1. To evaluate the efficacy of FDC against *T. trichiura* in paediatric population.<br>2. To evaluate the efficacy of FDC against hookworms and *S. stercoralis* in those co-infected with species concomitantly to their infections with *T. trichiura.*<br>3. To describe the extent of IVM exposure in different weight strata.<br>4. To evaluate the acceptability/palatability of the FDC 400mg-18mg and 400mg-9mg.<br><br>**<u>Phase III component</u>**<br>**Primary Objective:**<br>1. To evaluate the **efficacy** of the FDC as a single dose or 3-day single dose regimen compared to the standard single dose regimen of ALB (400 mg) for the treatment of *T. trichiura* in paediatric and young adult population.<br>**Secondary Objectives:**<br>1. To evaluate the **efficacy** of the FDC as a single dose or 3-day single dose regimen for the treatment of *T. trichiura*, hookworm and *S. stercoralis*. |

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| | 2. To evaluate the safety of the FDC as a single dose or 3-day dose regimen for the treatment of *T. trichiura*, hookworm and *S. stercoralis*.<br>3. To evaluate the performance of PCR in calculating the primary outcome measurement (efficacy) compared to an egg counting method (Kato-Katz and Baermann technique).<br>4. To evaluate the frequency of ALB resistance alleles in hookworm, *T. trichiura* and *S. stercoralis* in the three treatment arms before and after treatment.<br>**Exploratory Objectives:**<br>1. To assess the efficacy of the FDC against *A. lumbricoides* in co-infected participants compared to single dose ALB in participants co-infected with this STH.<br>2. To describe the efficacy of the FDC in the prevalence of scabies compared to single dose ALB 400 mg.<br>3. To evaluate the **efficacy** of the FDC in co-infected participants compared to single dose ALB in participants co-infected with STH. |
| **Endpoints:** | **<u>Phase II component</u>**<br>**Primary Endpoint:**<br>1. Frequency, type, severity and relationship to study drug for all adverse events and severe adverse events for a single dose of FDC and a 3-day Single Dose of FDC (safety).<br>**Secondary Endpoints:**<br>1. Measurement of Cure Rate (CR) for *T. trichiura* after the different treatment arms<br>2. Measurement of the Egg Reduction Rate (ERR) for *T. trichiura* after the different treatment arms<br>3. Measurement of CR for hookworm and *S. stercoralis* in those co-infected with species concomitantly to their infections with *T. trichiura.* |

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| | 4. Measurement of ERR for hookworm in those co-infected with species concomitantly to their infections with *T. trichiura.*<br>5. Measurement of the rate of absorption (Cmax), time to reach Cmax (Tmax) and extent of absorption (AUC) of the FDC and FDCx3.<br>6. Participant acceptability/palatability evaluation of the FDC 400mg-18mg and 400mg-9mg using the 5 point Likert/numeric rating scale (NRS).<br><br>**<u>Phase III component</u>**<br>**Primary Endpoints:**<br>1. Cure rate (CR) for *T. trichiura* 21 days after treatment, as determined by microscopy (efficacy *T. trichiura*).<br>**Secondary Endpoints:**<br>1. CR for hookworm and *S. stercoralis* 21 days after treatment, as determined by microscopy (efficacy hookworm and *S. stercoralis*).<br>2. ERR for *T. trichiura* 21 days after treatment, by microscopy.<br>3. Frequency, type, severity and relationship to study drug for all adverse events and severe adverse events for ALB, FDC and FDCx3 (safety).<br>4. CR for *T. trichiura,* hookworm and *S. stercoralis*, by PCR.<br>5. Parasite burden decrease after 21 days for *T. trichiura*, hookworm, and *S. stercoralis*, by PCR.<br>6. Evaluation of genotypic albendazole resistance in the three arms.<br>**Exploratory endpoints**<br>1. CR and ERR for *A. lumbricoides* in co-infected participants.<br>2. Prevalence of scabies before and after administration of ALB, FDC and FDCx3. |
| **Study Population:** | The estimated total number of participants for the adaptive design is 1223 (126 in the phase II and 1097 in the phase III component respectively). This sample size is powered to be able to measure efficacy for all three species in the adaptive design (625 participants for *T. trichiura*, 312 participants for |

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| | hookworm and 286 participants for *S. stercoralis*) assuming a 10% lost to follow-up rate.<br>The sample size for the phase II component is 20% of the total participants for *T. trichiura* (126 participants). The remaining 80% of the *T. trichiura* participants will be randomised in the phase III component. |
| **Eligibility criteria** | The study population will include male and female paediatric and young adults between 5 and 18 years-old that have *T. trichiura* for the case of the Phase II component and at least one of the following STH: *T. trichiura*, hookworm (considering both *A. duodenale* and *N. americanus*) and/or *S. stercoralis* for the phase III component. The eligibility criteria are as follows:<br>**Inclusion Criteria:**<br>Specific Phase II/Phase III<br>1. Phase II: Positive infection test by microscopy for *T. trichiura*<br>2. Phase III: Positive infection test by microscopy for at least one of the following STH: *T. trichiura*, hookworms and/or larvae of *S. stercoralis*.<br><br>Phase II and Phase III<br>3. Weight ≥15 Kg (for phase II and III) and ≤ 45kg (only phase II).<br>4. Male or female, aged 5 to 18 years.<br>5. Female participants who are ≥12 years old (or female post-menarche) must have a negative urine pregnancy test at screening or at the time of randomization.<br>6. Ability to take oral medication and willingness to comply with all study procedures.<br>7. Parental acceptance to participate in the study by obtaining a signed and dated informed consent form approved by the Regulatory authorities. In addition, written assent will be obtained from children aged 12–17 years.<br>**Exclusion Criteria:**<br>1. Intake of ALB, mebendazole and/or IVM three months before screening.<br>2. Currently receiving warfarin |

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| | 3. Residence outside the study area or planning to move away in the four weeks following recruitment.<br>4. Epidemiological risk of infection by *Loa loa*.<br>5. Serious medical illness, per investigator's criteria.<br>6. Any participant's condition that would prevent the appropriate evaluation and follow-up, as per investigator's criteria.<br>7. Known hypersensitivity to any components of either of the study treatment.<br>8. Positive pregnancy urine test, pregnant or first week post-partum. |
| **Description of Sites/Facilities Enrolling Participants:** | This study will be conducted in primary and secondary schools in Ethiopia, Kenya and Mozambique.<br>**Kenya (phase II and III components)**<br>The study will take place in Kwale county situated on the South coast of Kenya. It borders Tanzania to the South west, Taita taveta County to the West. The total area of the county is approximately 8,270 $Km^2$ with a population of about 760,897. The southern region of the county is on the shoreline of the Indian Ocean. The county is divided into four sub-counties, twenty wards (and thirty-four (34) locations. The county has 357 public primary schools (class 1-8). Stool and urine sample will be processed at the KEMR-Kwale laboratory.<br>**Ethiopia (phase III component only)**<br>The study will be conducted in the Bahir Dar Zurya woreda (district) in the West Gojam zone of the Amhara region which has an area of 1,443.37 $Km^2$, and a population of 230,000. The district has 36 primary (grade 1 to 8) and 6 secondary (grade 9 and 10) schools. The total number of student population is 49,013 with an average of 1,160 students in each school. Stool and urine samples will be processed at the BDU laboratory by competent laboratory technicians.<br>**Mozambique (phase III component only)**<br>The study will be conducted in the Manhiça district in Southern Mozambique, a peri-urban setting with a predominantly young population. The site runs a |

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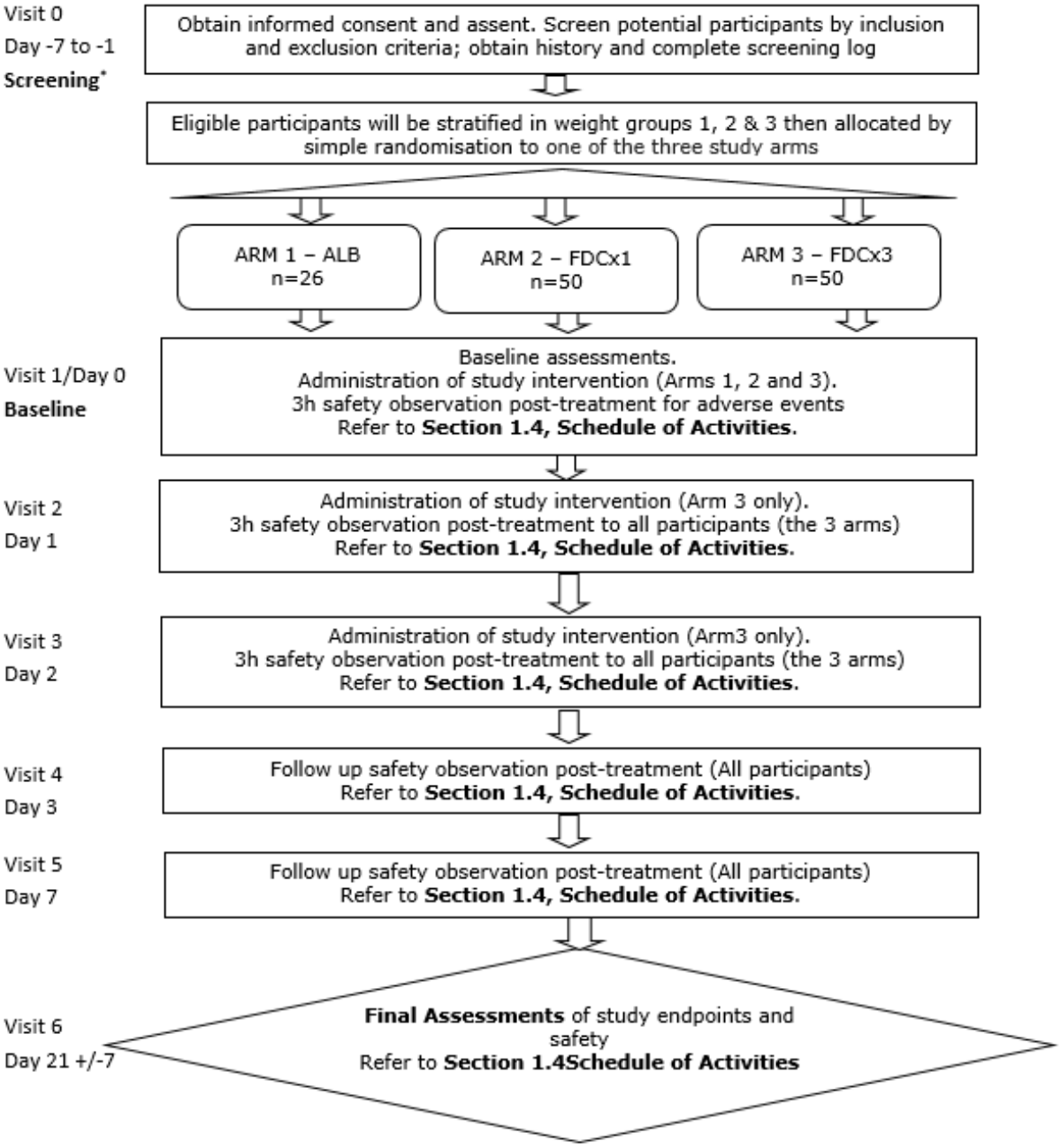
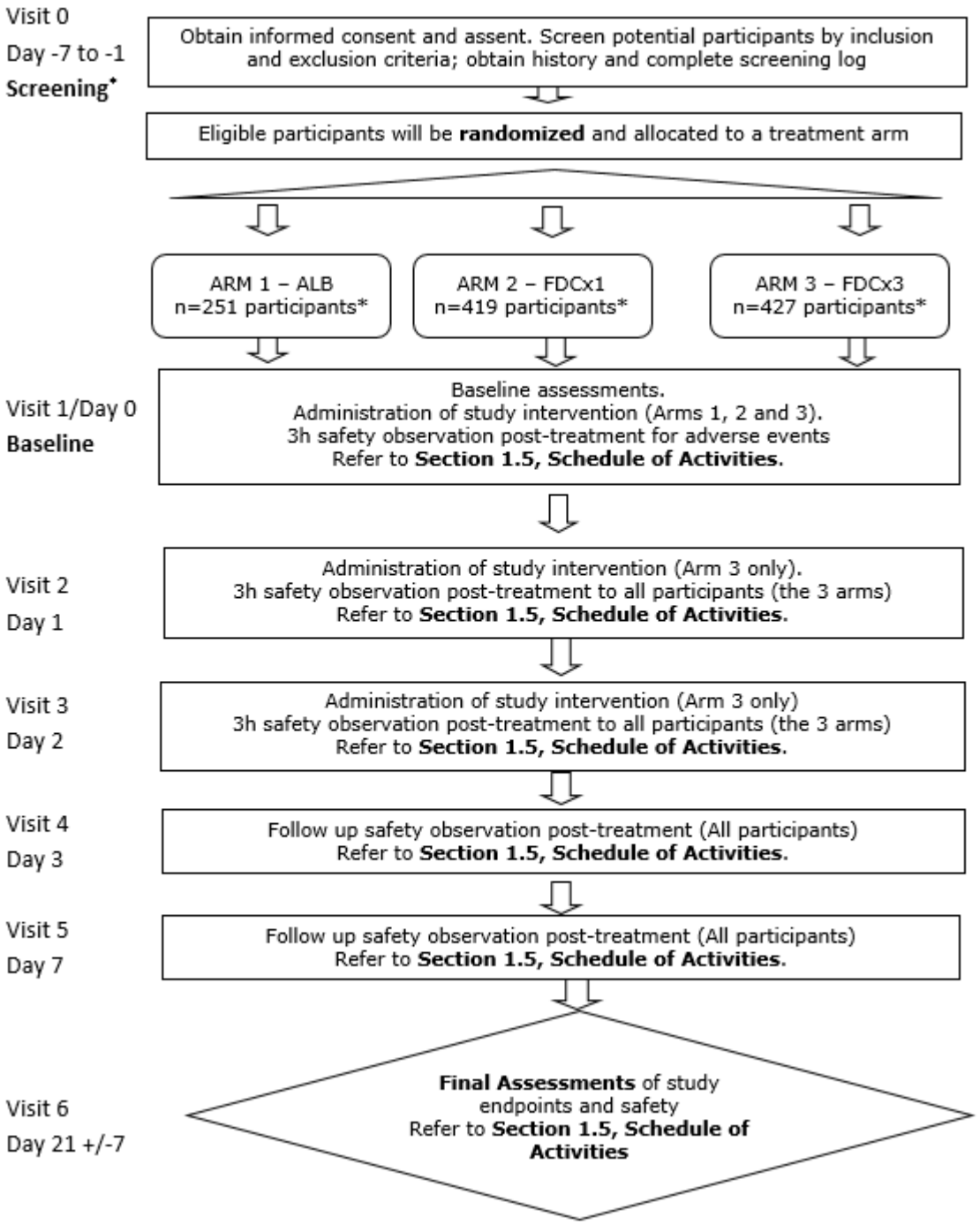
| | Demographic Surveillance System in the area which covers the entire district, with a population of ≈204,000 inhabitants under surveillance, 44% of which are <15 years of age. Every household from the study area is geo-localised with an identification number. The district has 93 primary and 9 secondary schools with a total student population of 72,829. Stool and urine samples will be processed at the FM-CISM laboratory by competent laboratory technicians.<br><br>At all sites, community sensitization will be conducted in the villages where the school children live by community health workers. Only children with informed consent and assent will be screened for eligibility and those who are eligible will be enrolled into the study. |
| **Description of Study Intervention:** | The FDC (ALB-IVM co-formulation), is an oral dispersible tablet and is the Investigational Medicinal Product (IMP) in this trial.<br>For participants <45 kg of body weight at baseline: FDC (400mg ALB-9mg IVM).<br>For participants ≥45 kg of body weight at baseline: FDC (400mg ALB- 18mg IVM. |
| **Study Duration:** | It is estimated that the study will take a total of 18 months from the First Patient First Visit (FPFV) in the phase II component to the Last Patient Last Visit (LPLV) in the phase III component.<br>Phase II→ Interim analysis* → phase III → interim efficacy analysis half-way during the phase III trial → final analysis at the end of the phase III component.<br>*Decision making on safety to move to the phase III component. |
| **Participant Duration:** | For each individual participant, the time to complete all study visits will be approximately 1 month. |

## 1.2 FLOW DIAGRAM PHASE II (KENYA)




*Group 1 (38 participants): with body weight of [23-<30) Kg will receive 300-391 µg/Kg (FDC 400mg-9mg) or ALB.
Group 2 (38 participants): with body weight of [30-45] Kg will receive 400-600 µg/Kg (FDC 400mg-18mg) or ALB.
Group 3 (50 participants): with body weight of [15-23) Kg will receive 391-600 µg/Kg (FDC 400mg-9mg) or ALB.
The estimated total number of participants for the **phase II component is 126**.

## 1.3 FLOW DIAGRAM PHASE III (KENYA, ETHIOPIA, MOZAMBIQUE)




*The estimated number of participants for the **phase III component is 1097**. And the estimated **total number of participants for the adaptive design is 1223** (*T. trichiura* 625, hookworm 312 and *S. stercoralis* 286).

## 1.4 SCHEDULE OF ACTIVITIES (SOA)/VISITS PHASE II (KENYA)

| **Procedures** | Pre-screening (up to 3 months prior scree.) | Study Visit 0 Screening Day -7 to -1 | Study Visit 1 Enrolment/ Baseline Day 0 | Study Visit 2/ Day 1 | Study Visit 3/ Day 2 | Study Visit 4/ Day 3 | Study Visit 5/ Day 7 | Study Visit 6 Day 21+/-7 day post treatment | Unscheduled | Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|
| Informed consent[a] | X | X | | | | | | | | |
| Informed assent[b] | X | X | | | | | | | | |
| Stool collection kit delivered | | X | | | | | | X | | |
| Stool collection[c] | | X | | | | | | X | | X |
| Stool analysis (Baermann and Kato-Katz)[d] | | X | | | | | | X | | X |
| Inclusion and Exclusion criteria | | X | X | | | | | | | |
| Demographics[e] | | X | | | | | | | | |
| Physical exam[f] | | X | X | | | | | X | X | X |
| Vital signs[g] | | X | X | X | X | X | X | X | X | X |
| Height | | X | X | | | | | | | |
| Weight | | X | X | | | | | | | |
| Urine Pregnancy test[h] | | X | | | | | | | | |
| Haematuria strip test for Schistosoma [h] | | X | | | | | | | | |
| Randomization and treatment assignation | | | X | | | | | | | |
| Study drug administration | | | X[i] | X[j] | [k]X | | | | | |
| Acceptability questionnaire Arm 2 (FDCx1) | | | X | | | | | | | |
| Acceptability questionnaire Arm (FDCx3) | | | | | X | | | | | |
| PK blood sampling | | | X[l] | X[l] | X[l] | | | | | |
| Study drug accountability | | | X | X | X | | | X | | X |
| Concomitant medication & disease review | | X | X | X | X | X | X | X | X | X |
| Adverse event monitoring[m] | | X | X | X | X | X | X | X | X | X |
| Complete Case Report Form (CRF) | | X | X | X | X | X | X | X | X | X |

[a] Informed consent will be obtained from parents or guardians of all participants <18years. Informed consent/assent can be performed up to 3 months prior to screening visit as part of the pre-screening activities OR during screening visit.

[b] Assent to participate in the trial will be obtained from participants 12-17 years old.

[c] A stool collection kit will be provided to participants for the collection of stool samples after providing assent and consent. The stool should be collected <24 h before examination for eligibility check. An aliquot of the collected stool sample will be stored for QC by PCR to confirm microscopic results from Kato-Katz and Baermann test if microscopy positive at screening and for all follow-up stool samples. All samples will be tested at site. Should technical issues arise or in case of discrepancy in results, an aliquot of the stool sample will be tested abroad for QC purposes.

[d] Lab tests will be performed on a fresh stool sample collected <24 hours before examination.

[e] Age, Date of Birth, Sex, Participant ID, Guardian relationship, age and contact details

[f] Physical exam should include clinical diagnosis of scabies (rush/lesions on skin) before and after treatment. During unscheduled visits Physical exam will be performed only if necessary.

[g] Vital signs should Include heart rate, respiration rate, body temperature and blood pressure.

[h] A urine test kit will be provided in order to collect a urine sample from which will be examined by a haematuria strip test as a proxy for *Schistosoma* and to confirm negative pregnancy test for female participants ≥12 years old or post-menarche.

[i] Treatment Day (D)0. For all participants in Arms 1, 2 and 3. Treatment dose will be given under direct supervision.

[j] Treatment D1. Only for participants in treatment Arm 3. Close observation for 3 hours post-treatment for safety evaluations

[k] Treatment D2. Only for participants in treatment Arm 3. Close observation for 3 hours post-treatment for safety evaluations.

[l] Population PK (2 timepoints per participant). for ALB arm at 1, 2, 3, 4, 5, 6, 7, 8, or 24h; for the single dose FDC arm at 1, 2, 3, 4, 5, 6, 7, 8, 24h, 48 or 72h; 2 timepoints for three-dose FDC arm at 1, 2, 3, 4, 5, 6, 7, 8, 24h, 48 or 72h post-administration and 1 additional timepoint at pre-dose Day 2..

[m] Adverse events will be assessed by direct observations of the study physician, or reported by the subject or parent/guardian.

## 1.5 SCHEDULE OF ACTIVITIES/VISITS (SOA) (PHASE III KENYA, ETHIOPIA, MOZAMBIQUE)

| **Procedures** | Pre-screening (up to 3 months prior scree.) | Study Visit 0 Screening Day -7 to -1 | Study Visit 1 Enrolment/ Baseline Day 0 | Study Visit 2/ Day 1 | Study Visit 3 Day 2 | Study Visit 4/ Day 3 | Study Visit 5/ Day 7 | Study Visit 6 Day 21+/-7 day post treatment | Unscheduled | Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|
| Informed consent[n] | X | X | | | | | | | | |
| Informed assent[o] | X | X | | | | | | | | |
| Stool collection kit delivered | | X | | | | | | X | | |
| Stool collection[p] | | X | | | | | | X | | X |
| Stool analysis (Baermann and Kato-Katz)[q] | | X | | | | | | X | | X |
| Inclusion and Exclusion criteria | | X | X | | | | | | | |
| Demographics[r] | | X | | | | | | | | |
| Physical exam[s] | | X | X | | | | | X | X | X |
| Vital signs[t] | | X | X | X | X | X | X | X | X | X |
| Height | | X | X | | | | | | | |
| Weight | | X | X | | | | | | | |
| Urine Pregnancy test[u] | | X | | | | | | | | |
| Haematuria strip test for Schistosoma [h] | | X | | | | | | | | |
| Serum HIV test[v] | | | | | | | | X | | |
| Randomization and treatment assignation | | | X | | | | | | | |
| Study drug administration | | | X[w] | X[x] | X[y] | | | | | |
| Study drug accountability | | | X | X | X | | | X | | X |
| Concomitant medication & disease review | | X | X | X | X | X | X | X | X | X |
| Adverse event monitoring[z] | | X | X | X | X | X | X | X | X | X |
| Complete Case Report Form (CRF) | | X | X | X | X | X | X | X | X | X |

[n] Informed consent will be obtained from parents or guardians of all participants <18years. Informed consent/assent can be performed up to 3 months prior to screening visit as part of the pre-screening activities OR during screening visit.

[o] Assent to participate in the trial will be obtained from participants 12-17 years old.

[p] A stool collection kit will be provided to participants for the collection of stool samples after providing assent and consent. The stool should be collected <24 h before examination for eligibility check. An aliquot of the collected stool sample will be stored for QC by PCR to confirm microscopic results from Kato-Katz and Baermann test if microscopy positive at screening and for all follow-up stool samples. Should technical issues arise or in case of discrepancy in results, an aliquot of the stool sample will be tested abroad for QC purposes.

[q] Lab tests will be performed on a fresh stool sample collected <24 hours before examination.

[r] Age, Date of Birth, Sex, Participant ID, Guardian relationship, age and contact details

[s] Physical exam should include clinical diagnosis of scabies (rush/lesions on skin) before and after treatment. During unscheduled visits Physical exam will be performed only if necessary.

[t] Vital signs should Include heart rate, respiration rate, body temperature and blood pressure.

[u] A urine test kit will be provided in order to collect urine sample from all participants which will be examined by haematuria strip test as a proxy *for* Schistosoma and to confirm negative pregnancy test for female participants ≥12 years old or post-menarche.

[v] Serum HIV test will be offered only to eligible participants at the Manhiça site in Mozambique because of high HIV prevalence.

[w] Treatment Day 0. For all participants in Arms 1, 2 and 3. Treatment dose will be given under direct supervision.

[x] Treatment Day 1. Only for participants in treatment Arm 3. Close observation for 3 hours post-treatment for safety evaluations.

[y] Treatment Day 2. Only for participants in treatment Arm 3. Close observation for 3 hours post-treatment for safety evaluations.

[z] Adverse events will be assessed by direct observations of the study physician, or reported by the subject or parent/guardian.

# 2 INTRODUCTION

## 2.1 STUDY RATIONALE

This clinical trial focuses on the search of new broad spectrum therapeutic approaches for the treatment of soil transmitted helminths (STH) for use in preventive chemotherapy (PC) through mass drug administration (MDA), as designed by the World Health Organization WHO(1). PC is defined by WHO, as a pharmacological intervention for the treatment of communities in order to prevent morbidity caused by the infections, but not as a means of preventing the acquisition of the infection. This trial will generate evidence-based information for decision making, WHO pre-qualification and the registration of a new anthelminthic co-formulation for the drug and medicines agencies in Africa and Europe (European Medicines Agency (EMA)).

STH are a group of diseases that include *Ascaris lumbricoides*, *Strongyloides stercoralis*, *Trichuris trichiura* and the hookworms: *Ancylostoma duodenale* and *Necator americanus*. Despite differences in their clinical syndromes and mechanisms of infection, they are all transmitted in areas with inadequate water and sanitation and hygiene measures. More than a quarter of the world's population is at risk of infection with STH. These diseases are the most prevalent of all Neglected Tropical Diseases (NTDs) worldwide and disproportionately affect impoverished populations, causing significant morbidity in pre-school and school age children(2). The 2015 Global Burden of Disease (GBD) study ranks STH as the NTD that poses the greatest burden of years lived with disability (YLD), with an estimation of 3.17 million years (3).

Currently, available treatments against STH are the benzimidazole drugs, albendazole (ALB) and mebendazole (MBZ), in single dose regimens because of their safety, efficacy and availability through drug donation from their manufacturers. Although the efficacy of ALB against *A. lumbricoides* remains above 90%, the efficacy against other STH species is estimated as 80% (95% CI: 72-86%) for hookworms and 31% (95% CI: 21-43%) for *T. trichiura* (4). It is particularly alarming that the efficacy against *T. trichiura* has decreased from 30% to 15% in the last 16 years (4). In addition, the currently recommended regimens against STH have very low efficacy against *S. stercoralis* (5), which remains largely untreated with the current WHO strategy. Given this situation, there is a pressing need to identify regimens with improved

efficacy and provide evidence for the revision of the current strategy, if transmission interruption goals are to be achieved (6,7).

The use of combination therapy with existing drugs against STH has been identified as a strategy that could offer a solution to the drawbacks and risks of the current strategy of monotherapy. Among them, the use of ALB-IVM has several advantages:

a. Vast experience in its use for the treatment of lymphatic filariasis (LF), with millions of individuals treated (8), without safety or drug interaction issues of clinical relevance.
b. Improved efficacy against *T. trichiura* and *S. stercoralis* (9,10).
c. Decreased risk of emergence of drug resistance due to the different mechanisms of action of the 2 components of the regimen (11,12).
d. Extended anti-parasitic spectrum with opportunities for integration with other NTD control programs (LF, scabies) and possibly malaria vector control (13).

As a reflection of the above-mentioned advantages, the WHO recently incorporated IVM to its list of essential drugs for the treatment of STH (14), and an expert panel gathered by the Bill & Melinda Gates Foundation identified ALB + IVM as the combination therapy to be explored in priority (15).

## 2.2 BACKGROUND

**Purpose and approach**

The purpose of this clinical trial is to evaluate a fixed-dose co-formulation (FDC) of IVM and ALB for the treatment of all STH (including *S. stercoralis*). This clinical trial is nested in a European and Developing Countries Clinical Trials Partnership (EDCTP) funded project called STOP whose overarching goal is to improve the effectiveness of MDA programmes against STH. Therefore, the STOP project will help achieve the goals established by the WHO to control the public health problems caused by STH, as well as the more ambitious goals of interrupting their transmission in affected communities (16–18). The innovative approach of this proposal is the use of fixed dose IVM co-formulated with ALB rather than weight-based IVM regimens. An added advantage of this innovative approach is the evaluation of 3-day regimen rather than single-dose regimens.

**Rationale for the use of high and fixed dose of IVM**

IVM is currently manufactured for human use in oral formulations (tablets) of 3 or 6 mg. Since the standard dosage is 150 or 200 µg/kg, a simple calculation must be done to know the number of tablets to administer a patient. The initiative to develop an alternative dosing regimen for IVM in a fixed-dose is based on the following concepts:

- IVM has demonstrated a wide therapeutic index, with hundreds of millions of doses distributed (at regular dosing) without toxicity issues (19,20).
- Current dosing strategies against onchocerciasis are based on the lack of increased efficacy with higher doses, but not due to toxicity issues (21).
- High-dose IVM is not a goal but rather a requisite for fixed dose co-formulation with ALB.
- Dosing of IVM is not based on target blood levels since no pharmacodynamic parameters have been determined in veterinary or human medicine. A possible exception is the estimated $LD_{50}$ calculated against *Anopheles gambiae* (15.9 to 22.4 ng/ml), but correlation with clinical impact on malaria has not been determined (22).
- Key pharmacokinetics characteristics of IVM to take into consideration are a high liposolubility and a high intra and interpersonal variability of bioavailability.
- Our group has demonstrated the safety and wide therapeutic range of IVM in a study with 54 healthy adult volunteers who received sequentially 200 µg/kg, a fix-dose of 18 mg and a fix-dose of 36 mg (using 18 mg IVM tablets manufactured by Laboratorios Liconsa), with no differences in type or severity of adverse events with doses of up to 700 µg/Kg (23).
- High doses of IVM have been tested in other studies and have shown an excellent safety profile: in adults, doses up to 10 times the 200 µg/kg have been tested in a small group of participants and showed the same rate of adverse events as placebo (24).
- Safety data on a single dose of 600µg/kg of IVM in adults and children have already been published (23,25). The safety profile of three consecutive daily doses of 600µg/kg of IVM has also been recently demonstrated in a clinical trial (26).
- Evidence in the literature on safety of ivermectin doses ≥200 and ≥400 µg/kg was thoroughly analyzed in a recent systematic review and meta-analysis which included trials administering up to 800µg/kg of ivermectin with very good tolerability. The meta-analysis component was performed with trials that included a control group receiving standard doses (150 to 200µg/Kg)

ivermectin which is also the most common dose recommended according to the summary of product characteristics for Stromectol (27).

- Five studies for a variety of indications were included in the meta-analysis using 400 µg/kg as the cut-off and no differences in the severity of the adverse events between standard ivermectin dose and doses higher than 400 µg/Kg were observed (Figure 1)(27)

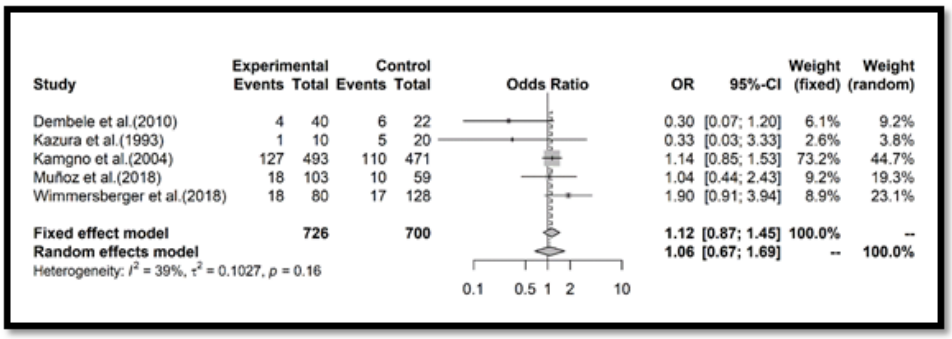



Figure 1. Meta-analysis of the association between AEs and standard- versus high-dose ivermectin using standard doses of 400 µg/kg

- The same systematic review also added evidence to the safety of ivermectin at doses up to 800 µg/kg, although this conclusion was based on a small number of studies and lack of blinding.
- Rationale for using the proposed FDC is also supported by the results of a recently published trial performed in Honduras where the safety and efficacy against pediatric *T. trichiura* infections was demonstrated in a pilot prospective, parallel-group, open-label randomized controlled clinical trial. In that trial evaluating the safety and efficacy of the concomitant administration of ALB 400mg + IVM 600µg/Kg either as a single dose or as daily dose for 3 consecutive days in comparison to ALB 400 mg (single dose or daily dose for 3 consecutive days respectively), the regimens containing high dose IVM achieved cure rates of 88.6% with a single dose and 100% in the 3-dose regimen; contrasting with a cure rate of 4% in the control arm (albendazole single dose). The safety assessment revealed no serious adverse events and 48 adverse events (AE) in the analyzed safety population (n: 175); those AEs were 85% mild and 15% moderate and the most frequent were headache and abdominal pain (28).

In children, doses of 400 µg/kg have been tested in clinical trials to evaluate treatment for head lice. This dosage was well tolerated, although 1.8% of participants (7 of 398) discontinued treatment because of adverse events (similar to control group receiving 0.5% malathion lotion) (29). Dose finding studies performed in Ivory Coast for the treatment of infections with *T. trichiura* in children have also demonstrated that regimens of 200, 400 and 600µg/Kg had adverse event rates similar to placebo (25) in terms of type, frequency and severity. The current use of IVM is restricted to populations ≥15 kg. This limitation, albeit not based on evidence demonstrating either lack of efficacy or added toxicity represents an obstacle in two different aspects of public health: 1. Excludes significant groups of the at-risk population from the benefits of IVM; 2. By lowering the absolute coverage of the interventions, it decreases the likelihood of transmission interruption and disease elimination.

**Rationale of a co-formulation**

Fixed-dose combinations are increasingly available due to their multiple benefits. They simplify drug administration and intake, lower manufacturing costs. For infectious diseases such as HIV and tuberculosis, combination therapies ensure the intake of all the drugs instead of only some, thereby decreasing the risk of treatment failure due to the emergence of drug resistance. For STH infection in endemic countries, MDA campaigns is the main control measure to deliver treatment to large populations and coverage rate is the principal outcome measure. Thus, the co-formulation proposed, will simplify MDA logistics and costs and ultimately allow for increased coverage rates.

In the case of the proposed FDC, the following conditions are met:

- Combination particularly ALB+IVM has been shown to enhance impact of STH control programmes on *T. trichuria* (30).
- Indication in combination for specific medical conditions (STH, LF).
- Key role in mass drug administration campaigns.
- Non-significant drug-drug interactions (31).
- Little impact on the size of the tablet since IVM is formulated in 3 and 6 mg tablets and ALB in 200 and 400 mg tablets.
- Favourable safety profile- millions of individuals have been previously treated with the components of the FDC at standard doses.

- Large target population. WHO reports from campaigns in 2015 had a target population of almost 700 million for LF and over 800 million against STH (some overlaps between both diseases), without including treatment of adults against STH (32).
- The combination may help prevent the emergence of drug resistance in a group of diseases without alternative treatments.
- High impact through the simplification of mass drug administration campaigns due to the double benefit of handling a single tablet and eliminating the need for weighing scales and dosing poles.
- Cost savings in manufacturing, packaging and distribution.

**Preliminary results of the FDC comparative bioavailability study**

A bioavailability study in healthy volunteers has been recently performed to compare the administration of IVM (Stromectol ® 3 mg tabs, 18 mg total dose) and ALB (Eskazole ® 400 mg). The trial was a single-center, single-dose, open-label, randomized, six-sequence, three-treatment, three-period crossover study in healthy male and nonpregnant female volunteers under light meal conditions. The primary objective was to characterize pharmacokinetic parameters and to assess the comparative bioavailability after a single dose under light meal conditions of the new fixed dose combination (FDC) of IVM/ALB 18 mg/400 mg in the form of oral dispersible tablets (Test Product), versus the Reference products Stromectol® (IVM 3 mg tablets) (Reference 1) and Eskazole® (ALB 400 mg tablets) (Reference 2). Doses of investigational products were separated by a washout interval of 28 calendar days. The secondary objective was to monitor the safety and tolerability of a single oral dose of investigational medicinal products mentioned before.

Comparable bioavailability was defined as point estimate of the mean ratio test/reference for AUC and Cmax within the 0.8-1.25 range. The higher strength 400 mg ALB-18 mg IVM was employed in this study under light meal conditions in 42 healthy adult volunteers.

Seventy-eight (78) subjects were enrolled and 66 subjects completed the study. Seventy-five (75) subjects had evaluable pharmacokinetic data on the Test product period. These subjects were included in the pharmacokinetic analysis population: pharmacokinetics of Test product. Seventy (70) subjects had evaluable pharmacokinetic data on the Test period and on the Reference 1 period. These subjects were included in the comparative bioavailability analysis population for IVM. Seventy (70) subjects had

evaluable pharmacokinetic data on the Test period and on the Reference 2 period. These subjects were included in the comparative biovailability analysis population for ALB.

The analytes of interest were H2B1a (97.2% of the total IVM), H2B1b (1.9% of the total IVM) for test product, and H2B1a: 99.0% - H2B1b: 1.5% for reference product Stromectol, ALB and ALB sulfoxide. $C_{max}$ and $AUC_{0-72}$ of $H_2B_{1a}$ and $H_2B_{1b}$ were the primary pharmacokinetic parameters for the comparison of bioequivalence for IVM. $C_{max}$ and $AUC_{0-t}$ of ALB and ALB sulfoxide were the primary pharmacokinetic parameters for the comparison of bioequivalence for albendazole.

The test /reference (T/R) geometric mean ration and the corresponding 90% Confidence Intervals for the primary PK metrics of interest are provided in Table 1.

Table 1. T/R GMR and the corresponding 90% Confidence Intervals for $C_{max}$ and AUC for $H_2B_{1a}$, $H_2B_{1b}$, Albendazole and Albendazole sulfoxide.

| | $H_2B_{1a}$ | $H_2B_{1b}$ | Albendazole | Albendazole sulfoxide |
|---|---|---|---|---|
| $C_{max}$ | 115.48 (110.68 – 120.49%) | 164.86 (155.87 – 174.37%) | 61.11 (53.10 – 70.34) | 76.56 (70.99 – 82.56) |
| $AUC_{0-72}$ | 114.94 (110.46 – 119.60%) | 169.80 (158.54 – 181.85%) | - | - |
| $AUC_{0-t}$ | - | - | 68.40 (61.13 – 76.54) | 81.13 (75.93 – 86.69) |

In summary, the Phase I study results revealed that for the moiety H2B1a the results regarding rate and extent of absorption indicate bioequivalence between Test and Reference, whereas for the moieties H2B1b, ALB and ALB sulfoxide bioequivalence could not be inferred. Importantly, concerning the secondary objective of safety and tolerability, no serious adverse event occurred during the bioequivalence study with only mild (n=51) and moderate (n=11) events reported, supporting the safety profile of the FDC.

Since the efficacy and safety of the new FDC product will be tested in the adaptive phase II/III trial, the obtained test/reference ratios are considered primarily "for description purposes only" and any incompliance with the 80-125% range is considered exceptionally still acceptable for the fixed drug combination (FDC) tablets as long as no major safety issues arose with the FDC in the Phase I study.

**Rationale for a 3-day regimen**

The current paradigm of MDA against helminths uses single day regimen, which is ideal for simplicity. However, current efficacy rates call this strategy into question (34). It has been shown that ALB increases its efficacy when used at repeated doses against hookworms and *T. trichiura* (33). Moreover, randomised clinical trials comparing 1, 2 or 3 days of ALB have shown improvements in cure rates (CR) against *T. trichiura* of up to 83% and hookworm of 93% in the 3-day group as compared to 40 and 54% respectively with single doses (35). In another study using 3-day regimens of ALB or MBZ against hookworms, the latter did not show significant improvements with the longer regimen but ALB increased its efficacy from 45 to 79% ($p<0.001$) (35). Steinmann *et al* in Yunnan, China also demonstrated that 3-day regimens of ALB or MBZ offered no advantage over the already highly effective single dose regimens against *A. lumbricoides*, while for hookworms and *T. trichiura* longer regimen achieved significant improvements in efficacy, achieving cure rates of 71% for *T. trichiura* in the 3-day regimen (36). Despite this improvement, the three day ALB regimens, would not supersede the additional benefits expected from the proposed FDC (IVM + ALB) and it must be emphasized that the FDC extends treatment coverage to population with *S. stercoralis*. Furthermore, in the interim analysis (70% of the study population) of a trial conducted in a hyperendemic area in Honduras, 1-day and 3-day ALB regimen, showed cure rates against *T. trichiura* at 4% (95%CI 0.2 - 23) for ALB 400mg single dose and 33% (95%CI 14 – 59%) for ALB 400mg for 3 days. This moderate improvement in efficacy is significantly lower than the preliminary results of the treatment arms containing ivermectin (*unpublished information*, *https://clinicaltrials.gov/ct2/show/NCT04041453*).

**Rationale for the adaptive design**

Adaptive clinical trial designs are based on the considerations that this design can make clinical trials more flexible and often more efficient, informative and they make better use of resources without lowering scientific and regulatory standards. Traditional or conventional clinical trials are run in three steps: design of the trial, conduct of the trial as per the design and finally data analyses according to a pre-specified analysis plan.

The proposed design comprises of firstly a phase II trial to evaluate safety and pharmacokinetics of the FDC. After analysis of the phase II component and conditional to the conclusions, the phase III component will be executed in the groups that best tolerate the FDC and this aligns with the flexible approach offered in adaptive trials such that changes can be made to the trial when necessary during the course of the trial.

An interim safety analysis will be performed before moving to phase III component to ensure safety of the dosage. The final analysis will take into account all the available data in the phase II and III components. An independent DSMB will analyse the data and suggest modifications for the trial in the event that the high doses of IVM are shown not to be safe.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

IVM is known to show an excellent safety profile except for those patients harbouring *Loa loa* infection (37). In recent studies, descriptions of transient minor visual disturbance were observed in the IVERMAL study (26). These events were reported to be mild, transient, and of short duration (a few minutes to a few hours) and in consistency with transient subjective ocular complaints reported in previous onchocerciasis studies. For this reason, in this study, participants will be observed closely for any immediate risks after study drug administration particularly for participants in Arm 2, receiving three consecutive doses of the FDC. No long-term risks are foreseen. More recently, a pilot prospective, parallel-group, open-label randomized controlled clinical trial evaluating the safety and efficacy of the concomitant administration of ALB 400mg + IVM 600µg/Kg either as a single dose or as daily dose for 3 consecutive days in comparison to ALB 400 mg (single dose or daily dose for 3 consecutive days respectively) in Honduras (*Clinical trial NCT04041453)*, showed no relevant differences in the safety of the active arms in comparison with the control arms.

### 2.3.2 KNOWN POTENTIAL BENEFITS

The use of ALB-IVM in the proposed fixed-dose combination therapy against STH could offer a solution to several disadvantages and risks of the current strategy in terms of efficacy, spectrum, prevention of drug resistance and logistics of administration as described in section 2.2, as well as treatment cost, which despite being beyond the scope of the current trial, will be measured in pharmacoeconomic studies within the STOP project.

### 2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

In this trial, a fixed dose co-formulation of ALB-IVM will be tested in primary and secondary school age group population. The potential benefits of the proposed drug combination outweigh the potential known risks.

A recent report of the WHO Expert Committee on Selection and Use of Essential Medicines acknowledged the favourable benefit to harm ratio of IVM, and its potential impact on the treatment of STH, including *S. stercoralis*.(38) The report highlighted the benefits of the use of IVM in combination with ALB which has an excellent safety profile. The combination strategy, has an added advantage of decreasing the possibility of emergence of resistance. Combination therapy is considered the most promising tool to shift from control of morbidity towards interruption of transmission of STH as shown in recent mathematical models.(39)

The proposed FDC has the potential to improve the health of millions of children and adults by decreasing morbidity caused by parasitic infections.

# 3 OBJECTIVES AND ENDPOINTS

**Hypothesis**

We hypothesise that the FDC (either at single or 3-day regimens) will be more effective against STH compared to the current strategy (single dose ALB alone).

| OBJECTIVES | ENDPOINTS |
|---|---|
| Phase II component | |
| Primary | |
| 1. To evaluate the **safety** of the FDC as a single dose or three-dose regimen for the treatment of *T. trichiura* in paediatric and young adult population. | 1. Frequency, type, severity and relationship to study drug for all adverse events and severe adverse events for FDC and FDCx3 (safety). |
| Secondary | |
| 1. To evaluate the efficacy of FDC against *T. trichiura* in paediatric population.<br>2. To evaluate the efficacy of FDC against hookworms and *S. stercoralis* in those co-infected with species concomitantly to their infections with *T. trichiura.*<br>3. To describe the extent of ivermectin exposure in different weight strata.<br>4. To evaluate the acceptability/palatability of the FDC 400mg-18mg and 400mg-9mg. | 1. Measurement of CR for *T. trichiura* after the different treatment arms<br>2. Measurement of the ERR for *T. trichiura* after the different treatment arms<br>3. Measurement of CR for hookworm and *S. stercoralis* in those co-infected with species concomitantly to their infections with *T. trichiura.*<br>4. Measurement of ERR for hookworm in those co-infected with species concomitantly to their infections with *T. trichiura.*<br>5. Measurement of the rate of absorption (Cmax), time to reach Cmax (Tmax) and extent of absorption (AUC) of the FDC and FDCx3.<br>6. Participant acceptability and palatability evaluation of the FDC 400mg-18mg and 400mg- |

| OBJECTIVES | ENDPOINTS |
|---|---|
| | 9mg using the 5 point Likert/numeric rating scale (NRS). |
| Phase III component | |
| Primary | |
| 1. To evaluate the **efficacy** of the FDC as a single dose or 3-day single dose regimen compared to the standard single dose regimen of ALB (400 mg) for the treatment of *T. trichiura* in paediatric and young adult population. | 1. Cure rate (CR) for, *T. trichiura* 21 days after treatment as determined by microscopy (efficacy *T. trichiura*). |
| Secondary | |
| 1. To evaluate the **efficacy** of the FDC as a single dose or 3-day single dose regimen for the treatment of hookworm and *S. stercoralis*.<br>2. To evaluate the safety of the FDC as a single dose or 3-day dose regimen for the treatment of *T. trichiura*, hookworm and *S. stercoralis*.<br>3. To evaluate the performance of PCR in calculating the primary outcome measurement (efficacy) compared to an egg counting method (Kato-Katz).<br>4. To evaluate the frequency of known ALB resistant alleles in hookworm and *T. trichiura* in the three treatment arms before and after treatment. | 1. CR for hookworm and *S. stercoralis* 21 days after treatment, as determined by microscopy (efficacy hookworm and *S. stercoralis*).<br>2. Egg reduction rate (ERR) for *T. trichiura* 21 days after treatment by microscopy.<br>3. Frequency, type, severity and relationship to study drug for all adverse events and severe adverse events for ALB, FDC and FDCx3 (safety).<br>4. CR for hookworm, *T. trichiura* and *S. stercoralis* using PCR.<br>5. Parasite burden for hookworm, *T. trichiura* and *S. stercoralis* by PCR.<br>6. Evaluation of genotypic albendazole resistance in the three arms. |
| Exploratory | |
| 1. To assess the efficacy of the FDC against *A. lumbricoides* in co-infected participants | 1. CR and ERR for *A. lumbricoides* in co-infected participants. |

| OBJECTIVES | ENDPOINTS |
|---|---|
| compared to single dose ALB in participants co-infected with this STH.<br>2. To describe the efficacy of the FDC in the prevalence of scabies compared to single dose ALB 400 mg.<br>3. To evaluate the **efficacy** of the FDC in co-infected participants compared to single dose ALB in participants co-infected with STH. | 2. Prevalence of scabies before and after treatment administration of ALB, FDC and FDCx3. |

**Primary outcome measures**

**Safety evaluations:** Safety evaluations and measurements, including adverse events, vital signs, physical examination, weight, height and BMI will be assessed after signing the informed consent through to post-treatment follow-up visit. To evaluate safety, participants will be evaluated as detailed in the SOA. All adverse events during all study visits, will be noted in the source documents for each participant. A close surveillance, 3 hours post-treatment, will be conducted each day a participant receives study treatment. Any clinically significant abnormalities persisting at the end of the study will be followed up by the study physician until resolution or until a clinically stable endpoint is reached.

A Data Safety Monitoring Board (DSMB) will monitor the ongoing safety of the participants during the study. The following stopping rules will apply at relevant key instances in the ALIVE study:

1. The occurrence of ≥1 serious adverse reaction (where causality is at least possible) or SUSAR in any of the weight groups in the Phase II will result in suspension of dose escalation in the FDC arm pending review by the DSMB (keeping in mind the sequential recruitment strategy in phase II).
2. The occurrence of ≥2 serious adverse reactions or SUSARs at the end of phase II will result in suspension of progress to phase III pending review by the DSMB.

Overall the occurrence of serious adverse reactions or SUSARs in 2% of the study populations at interim analysis (50% recruitment) will result in suspension of further dosing of the Investigational Product

pending review by the DSMB. This is equivalent to 12 safety events which meet these criteria in 612 subjects recruited at the point of the interim analysis.

**Efficacy evaluation**: Anti-helminthic primary efficacy, measured by cure rate will be determined by analysing a stool sample taken 21(+/-7) days after completing treatment with Kato Katz, Baermann and PCR. (18,40). Cure is defined as absence of the species of STH in participants who had a positive egg count and/or larva for that STH at baseline. Cure rate (CR) is defined as the proportion of individuals cured (absence of any egg) to the total of those infected at baseline with each particular species of STH.

**Secondary outcome measures**

**Treatment efficacy:** Anti-helminthic efficacy, measured through egg reduction rate (ERR), will be determined by analysing a stool sample taken 21(+/-7) days after completing treatment with Kato Katz, Baermann and PCR (40). Egg reduction rate (ERR) will be calculated by using geometric means, calculated for hookworms, *T. trichiura* and *A. lumbricoides*.

At pre- and post-treatment visits a duplicate Kato-Katz test will be performed on a fresh stool sample collected <24 hours before examination. Baermann method will also be performed in parallel to Kato-Katz for the search of *S. stercoralis*. Evaluation by PCR will be performed in pre- and post-treatment samples.

**Pharmacokinetic outcome measures:** Two blood samples for population PK analysis will be collected for every participant by finger prick using the mitra devices (41) in the phase II component to cover the following timepoints to determine FDC concentrations (Cmax), time to reach Cmax (Tmax) and area under the curve (AUC):

- ALB arm: 1, 2, 3, 4, 5, 6, 7, 8, 24h after treatment administration.
- FDC Single dose arm: 1, 2, 3, 4, 5, 6, 7, 8, 24, 48, 72h after treatment administration.
- FDC Three-day arm: 1, 2, 3, 4, 5, 6, 7, 8, 24, 48, 72h after treatment administration (time points considered respective to the last dose on Day 2). In this group, 1 additional timepoint will be collected at Day 2 pre-dose.

Refer to Section 8.2 for additional information on population PK.

**Participant acceptability/palatability outcome measures:**

Facial hedonic scale and implied numerical rating scale (NRS) will be included in the Phase II component of the trial to measure attributes for the FDC orodispersible formulation in terms of taste, aftertaste; mouth feel; smell; time needed to dissolve/disperse (duration of administration). Secondary aspects will include visual aspects: embossing, surface aspects and colour. Refer to Section 9.5.2 for details.

**Resistance:** Whole genome sequencing, next-generation DNA sequencing and omic approaches will be used to assess underlying factors associated with low treatment response including assessment and evaluation of new protocols for sample processing and sequencing.

# 4 STUDY DESIGN

## 4.1 OVERALL DESIGN

**Study phase and classification**

This will be an adaptive phase II/III trial to compare safety and efficacy of the active control arm (current standard of care) against 2 experimental arms.

**Phase II component**

Uni-centric, 3-arm, parallel, open-label, randomised, phase II trial to determine the safety and tolerability of FDC in paediatric population in different weight strata. Stratification by weight thus recruiting sequentially for safety and tolerability.

- Group 1 (38 participants): with body weight of [23-<30) Kg will receive 300-391 µg/Kg (FDC 400mg-9mg) or ALB.
- Group 2 (38 participants): with body weight of [30-45] Kg will receive 400-600 µg/Kg (FDC 400mg-18mg) or ALB.
- Group 3 (50 participants): with body weight of [15-23) Kg will receive 391-600 µg/Kg (FDC 400mg-9mg) or ALB.

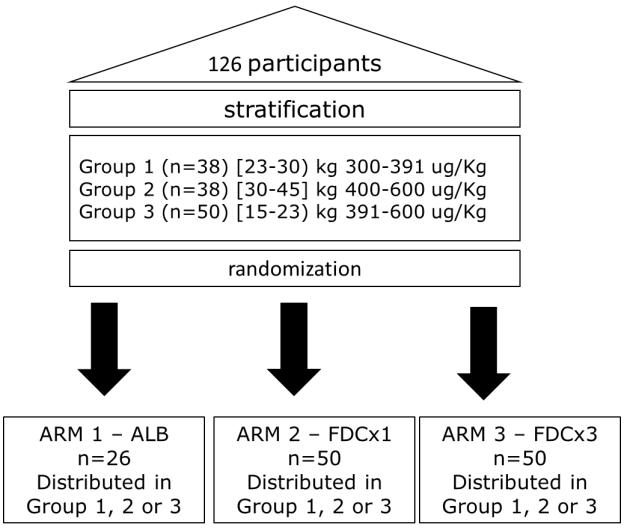



Figure 2. Phase II design (Kenya)

A conservative staged approach to weight-groups 1 through 3 will be taken. Enrolment will be sequentially done between weight groups 1 through 3, randomizing for all 3 treatment arms. Once weight group 1 is complete full source document verification of safety data up to Day 7 will be done and data will be shared with the DSMB and reviewed. If the stopping rule is not met, the DSMB will provide clearance to proceed with enrolment to the following weight group.

Once finalized recruitment of weight group 3, if safety data suggest that doses up to 600 µg/kg of ivermectin for 3 days are possible, then the DSMB will provide clearance to proceed to the phase III component in order to evaluate safety and efficacy of the FDC when given for 1 or 3 days across the target age/weight range.

**Phase III component**

A Single-Blinded, Randomized, Multi-Centre, Parallel-Group, Active-Controlled, Superiority Study to Evaluate the Efficacy and Safety of a Single Day or 3-day Single Dose of FDC for the treatment of *Trichuris trichiura*, hookworm, *Strongyloides stercoralis* in paediatric and young adult population.

a. Arm 1: Single dose of a tablet of ALB 400 mg (active control arm)
*b.* Arm 2: Single dose of a tablet of FDC 400mg-18mg (≥45 kg of body weight at baseline) or 400mg-9mg (<45 kg of body weight at baseline).
c. Arm 3: Daily dose of a tablet of FDC 400mg-18mg (≥45 kg of body weight at baseline) or 400mg-9mg for 3 days (<45 kg of body weight at baseline).

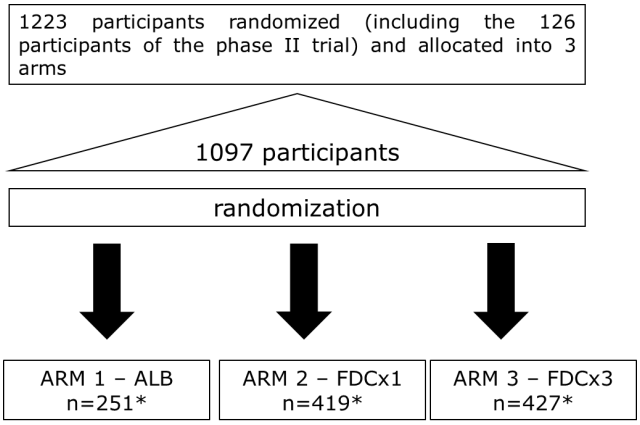



Figure 3. phase III design (Kenya, Ethiopia, Mozambique)

**Method of Allocation**

In the phase II component, participants with *T. trichiura* infection (confirmed by Kato-Katz technique in a fresh stool sample) will be enrolled in a sequential manner per weight group in order to administer the desired dose, starting from 300-391 µg/kg ivermectin. Participants in the phase II trial will be stratified in different weight groups: Group 1 (23-<30 kg) 38 participants, group 2 (30-45 kg) 38 participants and group 3 (15-23 kg) 50 participants in order to gradually increase the dose of ivermectin in the FDC. Then, participants will be allocated by simple randomization to one of the three study arms (ALB, FDCx1 and FDCx3).

In the phase III component, allocation of participants to study arms will be done by block randomization and stratified by STH species. We will ensure balanced allocation to the three arms in the three study countries. Treatment allocation for each study participant will be concealed in opaque sealed envelopes that will be opened only after enrolment. Study participants will be assigned a unique study number linked to the allocated treatment group. The allocation ratio for the three study arms will be 1:1:1.

**Blinding**

The study design has a blinded assessment for the primary endpoint, which is a laboratory-based measurement to be performed by blinded operators who will receive coded samples. Although a double-blind design would be better, this would imply that the participants in two of the three treatment arms would have to swallow multiple placebo tablets, which could lead to unnecessary complications and possible dropouts.

**Study arms**

Phase II component

- **Treatment Arm 1:** Single dose of a tablet of ALB 400mg.
- **Treatment Arm 2**: Single dose of a tablet of FDC 400mg-18mg or 400mg-9mg (based on weight group).
- **Treatment Arm 3:** Daily dose of a tablet of FDC 400mg-18mg or 400mg-9mg for 3 days (based on weight group).

Phase III component

- **Treatment Arm 1:** Single dose of a tablet of ALB 400 mg (active control arm).
- **Treatment Arm 2**: Single dose of a tablet of FDC 400mg-18mg or 400mg-9mg.
    - For participants <45 kg of body weight at baseline: FDC of 400mg ALB-9mg IVM.
    - For participants ≥45 kg of body weight at baseline: FDC of 400mg ALB-18mg IVM.

- **Treatment Arm 3**: Daily dose of a tablet of FDC 400mg-18mg or 400mg-9mg for 3 days.
    - For participants <45 kg of body weight at baseline: FDC of 400mg ALB-9mg IVM.
    - For participants ≥45 kg of body weight at baseline: FDC of 400mg ALB-18mg IVM.

Interim analysis is planned for this study. Refer to details in Section 9.4.6 (Planned Interim Analysis).

## 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

**Rationale for randomization of treatment groups**

Randomization will be used to minimize bias in the assignment of participants to any of the three groups, to increase the likelihood that known and unknown subject attributes (e.g. demographic and baseline characteristics) are evenly balanced between groups, and to enhance the validity of statistical comparisons across treatment groups.

**Rationale for not including participants with a single infection with *A. lumbricoides***

Due to the known good sensitivity of *A. lumbricoides* to ALB (current stand of care), participants who are only infected with this parasite will not be enrolled since no extra benefit is expected to be achieved with the FDC for this population. Moreover, in order to detect differences among treatment groups if participants with *A. lumbricoides* are included will mean a vast increase in the sample size which is unaffordable. Evaluation of participants with *A. lumbricoides* is an exploratory endpoint for those participants who are also infected with either hookworm*, T. trichiura* or *S. stercoralis*.

**Rationale for not including an IVM stand-alone arm**

For the endpoints of the phase III trial, an ivermectin arm is not necessary firstly because it is not efficacious against *T. trichiura* (25) and hookworm in monotherapy. Although ivermectin is efficacious against *S. stercoralis*, the purpose of the FDC is to target a relevant public health burden of STH by

adopting a wide spectrum approach. Thus, the proposed FDC in the context of MDA, will tackle infections caused by *T. trichiura* (primary objective of the trial), hookworm and *S. stercoralis* (secondary objectives). Secondly, considering the low efficacy of ivermectin for *T. trichiura* and hookworm, it will not be ethically justifiable to perform a trial with an ivermectin alone arm when there will be no beneficence for the participants that fall into that arm. Furthermore, scientific evidence suggests and recommends combination therapy with existing drugs against STH (42,43).

**Rationale for Site Selection**

All recruiting institutions are based in Africa and are partners and collaborators of the EDCTP-funded STOP project. Sites were invited based on experience with Good Clinical Practice (GCP), prevalence of the disease, extensive experience with IVM and ALB and ability to conduct the study in the required timeframe with the necessary number of participants.

**Rationale for Study Population Selection**

Participants between 5 and 18 years of age will be screened. This age range has been selected because of the high prevalence of STH in this population (it is the group most affected with STH), and the beneficial logistics implications of recruiting/enrolling at schools. The total number of participants to be screened depends on the prevalence rates of STH at the study site(s). A participant infected with a mixture of worms will be counted in the sample size for each worm that the participant is infected.

## 4.3 RATIONALE FOR DOSE

**Albendazole (ALB) in Active control arm**

Albendazole, through drug donations, is (along with mebendazole) the current standard of care for public health interventions for the control of STH as a public health problem. The recommended regimen is 400mg in single dose for individuals ≥2 years old. The safety of this drug in the regimen proposed for this clinical trial has been extensively evaluated and is a mainstay in MDA campaigns against LF and STH with negligible adverse events (1,44). The excellent safety profile allows to perform administration by non-health personnel during MDA activities (45). Choking in young children is the most frequent adverse event, therefore chewable formulations are routinely used.

**Fixed Dose Co-formulation (FDC)**

The fixed dose co-formulation is composed of ALB and IVM. IVM has a wide therapeutic index, and has shown an excellent safety profile (36). Most of the severe adverse events of IVM have been described in patients with *Loa loa* microfilaremia, which has been associated to the death of numerous microfilariae and can produce life threatening events, especially encephalopathy (46). Otherwise, after administering a cumulative more than 1.32 billion treatments in mass drug administration programs mainly in Sub-Saharan Africa, it has been proven that IVM is a remarkably safe drug in humans. Most adverse side effects are minor, including mild gastrointestinal symptoms, dizziness, fatigue, and cutaneous allergic reactions. Biochemical abnormalities such as elevated liver enzymes and leukopenia are rarely seen (24,26,47,48).

Although IVM does not usually cross the blood-brain barrier, there are concerns about the possible neurotoxicity in case of an immature blood-brain barrier. Thus, IVM is generally not recommended for use in children under 3 or 5 years of age (depending on the country) or weighing less than 15 kg, in pregnancy and lactation, or in patients with diseases of the central nervous system. Still, a recently published individual patient data meta-analysis of children weighting less than 15 kg, including 1088 children, identified 18 adverse events (all mild and self-limiting) in 15 children (1.4%) (49). Recent data showed that IVM could be safe in younger children, even when administered at higher doses (29). There is a need to provide data about safety and pharmacokinetics (PK) of IVM in children younger than 5 years to allow for a broader use of the drug in patients who need it, given the high prevalence of several pathologies that could be managed with IVM in this age group.

FDC co-formulation of ALB and IVM is expected to have a safety profile similar to the co-administration of the drugs as delivered in MDA programs and clinical trials (50, 51). The high-fixed dose, as explained above in section 2.2, has been explored in a healthy volunteer study without added toxicity. Results from the comparative bioavailability study recently performed also support the safety profile of the FDC proposed in this phase II/III adaptive design. The safety results in the phase II component will guide the dose to be used in the phase III component. The phase II component will also provide data on the PK parameters of the FDC.

For this trial, the route of administration of the FDC is via oral dispersible tablets in either a one or three-dose regimen.

## 4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit (study visit 6, Day 21 +/- 7 days) and scheduled procedures shown in the SOAs.

Although study participation ends at the follow-up visit 6 (21 days post-treatment), participants still harbouring STH at the follow-up visit will be referred for medical care at the local health reference centre for care. The drug of choice for treatment (ALB or IVM) will be provided free of charge.

# 5 STUDY POPULATION

## 5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

Specific Phase II/Phase III

1. Phase II: Positive infection test by microscopy for *T. trichiura*
2. Phase III: Positive infection test by microscopy for at least one of the following STH: *T. trichiura* hookworms, and/or larvae of *S. stercoralis*.

To be applied to Phase II and Phase III:

1. Weight ≥15 Kg (for phase II and III) and ≤ 45kg (only phase II).
2. Male or female, aged 5 to 18 years.
3. Female participants who are ≥12 years old (or female who is post-menarche) must have a negative urine pregnancy test at screening or at the time of randomisation.
4. Ability to take oral medication, willingness to comply with all study procedures.
5. Parental acceptance to participate in the study by obtaining a signed and dated informed consent form approved by the Regulatory authorities. Written assent will also be obtained from children aged 12–17 years.

## 5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Intake of ALB, mebendazole and/or IVM within the previous 3 months before screening.
2. Currently receiving warfarin.
3. Residence outside the study area or planning to move away in the four weeks following recruitment.
4. Epidemiological risk of *Loa loa* infection.
5. Serious medical illness, per investigator's criteria.
6. Any participant's condition preventing from the appropriate evaluation and follow-up, as per investigator's criteria.
7. Known hypersensitivity to any component of either study treatment.
8. Positive urine test, pregnant or first week post-partum.

## 5.3 LIFESTYLE CONSIDERATIONS

During this study, participants will be asked to refrain from eating grapefruits or drinking grapefruit juice until study completion. Participants will be advised to have a light meal prior to study drug administration.

## 5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. For all screen failures, a minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. A screening log with minimal information will be collected for all participants that are screened. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) recorded upon signing the informed consent form and followed up until resolution.

## 5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment will be performed at schools and in the communities. No participant will be excluded from participation because of sex, race, or ethnicity or HIV status. The randomization process will ensure a balanced allocation of male and female participants in the trial.

Community mobilization and sensitization will be done by community health workers in the study area of each recruiting institution. The basic concepts about helminth infections, risk factors and prevention measures and available treatments will be shared with the community during this initial process. The main purpose of the clinical trial, and the activities foreseen will be explained to teachers, community leaders, and parents. Then, participants and/or legal representative or guardians/caretakers will be asked whether they are willing to participate to the study protocol.

The strategy to conduct the study in schools will help in the retention of participants for the study, however, recruitment will also be conducted at the community (house hold) level in order to reach the total number of participants needed for the trial. The short and focalized follow-up period will facilitate retention during the trial and minimize lost to follow-up of participants. For school recruitment, the school

calendar and timetables will be considered for scheduling the clinical trial visits in order to minimise interruption of scheduled activities.

House visits will be performed for study participants who miss school days on study-visits, in order to determine the cause of absenteeism and document any adverse events. A specific team will be identified and adequately trained to conduct these activities before the beginning of the trial.

The estimated total number of participants for the adaptive design is 1223 (*T. trichiura* 625, hookworm 312 and *S. stercoralis* 286). This sample size is powered to be able to measure efficacy for all three species in the phase III component, assuming a 10% lost to follow-up rate. The sample size for the phase II component is 20% of the total participants for *T. trichiura* (126 participants). The remaining 80% of the *T. trichiura* participants will be randomised in the phase III component. The total duration of the trial will be 18 months.

**Justification for inclusion of children**

The study population is children and young adults within the ages of 5 to 18. Current WHO Guidelines for Preventive Chemotherapy (PC) to control STH infections target at risk population groups, specifically young-children (12-23 months of age), pre-school age children (PSAC) (24-59 months of age) and school-age children (SAC) (5 to 12 or 14 years of age) living in areas where the baseline prevalence of any STH ≥ 20%. The Guidelines also includes pregnant women after the first trimester, non-pregnant adolescent girls (10-19 years of age) and non-pregnant women of reproductive age (15-49 years of age) living under similar epidemiologic conditions as those explained above for children (52). The prioritization of the above-mentioned groups is justified by the particular vulnerability of children to the morbidity caused by STH, with consequences in growth (10) and development. Recently updated information by WHO shows steady progress in the number of individuals achieved by these interventions, in a total of 101 countries requiring PC against STH for over 272 million PSAC and over 596 million SAC requiring PC worldwide, of whom approximately 69% were reached in 2017 according to WHO reports (53). Those children requiring PC for STH comprises of over 50% of the total target population, based on the WHO reports, and are therefore those that will mostly benefit from improvements in efficacy and in the logistic and economic advantages provided by regimens that allow larger coverage rates at diminished cost per treatment, as proposed by the innovative formulations and dosing strategies of this clinical trial. At the same time, the generation of evidence of safety and acceptability is also necessary in these age groups if an impact in the WHO Guidelines is sought.

# 6 STUDY TREATMENT

## 6.1 STUDY TREATMENT ADMINISTRATION

### 6.1.1 STUDY TREATMENT DESCRIPTION

FDC of ALB-IVM (400mg-18 mg and 400mg-9mg) will be developed and manufactured under Good Manufacturing Practices (GMP) by Laboratorios Liconsa, who will be responsible for the pharmaceutical development of the fixed-dose co-formulation and subsequent production, labelling, packaging and distribution to the trial sites.

For the control medication (study Arm 1), commercially available Albendazole tablets 400 mg manufactured under GMP will be provided by Laboratorios Liconsa for use in this study in accordance with approved labelling.

### 6.1.2 DOSING AND ADMINISTRATION

Phase II component

Participants will be randomly allocated with equal probability to receive either:

Treatment Arm 1: Single dose of a tablet of ALB

Treatment Arm 2: Single dose of a tablet of FDC

Treatment Arm 3: Daily dose of a tablet of FDC for 3 days.

and will be recruited by µg/Kg of IVM to be received in a sequential manner starting from Group 1 through to Group 3 as shown below:

- Group 1: receiving 300-391 µg/Kg or ALB 400mg- 38 participants (body weight: 23-<30 Kg) will be recruited in this group. (FDC 400mg-9mg).
- Group 2: receiving 400-600 µg/Kg or ALB 400mg– 38 participants (body weight: 30-45 Kg) will be recruited in this group. (FDC 400mg-18mg).
- Group 3: receiving 391-600 µg/Kg or ALB 400mg- 50 participants (body weight: 15-23 Kg) will be recruited in this group. (FDC 400mg-9mg).

Group 2 will receive FDC in an Albendazole 400mg/Ivermectin 18mg comp, groups 1 and 3 will receive FDC in an Albendazole 400mg/Ivermectin 9mg comp.

The table below shows the equivalent dose adjusted per weight received from 15 to 45 kg:

| **Weight (Kg)** | **Ivermectin Dose** | Equivalent dose received (µg/Kg) | | Weight (Kg) | Ivermectin Dose | Equivalent dose received (µg/Kg) |
|---|---|---|---|---|---|---|
| ***15*** | 9 | 600 | | ***31*** | 18 | 581 |
| ***16*** | 9 | 563 | | ***32*** | 18 | 563 |
| ***17*** | 9 | 529 | | ***33*** | 18 | 545 |
| ***18*** | 9 | 500 | | ***34*** | 18 | 529 |
| ***19*** | 9 | 474 | | ***35*** | 18 | 514 |
| ***20*** | 9 | 450 | | ***36*** | 18 | 500 |
| ***21*** | 9 | 429 | | ***37*** | 18 | 486 |
| ***22*** | 9 | 409 | | ***38*** | 18 | 474 |
| ***23*** | 9 | 391 | | ***39*** | 18 | 462 |
| ***24*** | 9 | 375 | | ***40*** | 18 | 450 |
| ***25*** | 9 | 360 | | ***41*** | 18 | 439 |
| ***26*** | 9 | 346 | | ***42*** | 18 | 429 |
| ***27*** | 9 | 333 | | ***43*** | 18 | 419 |
| ***28*** | 9 | 321 | | ***44*** | 18 | 409 |
| ***29*** | 9 | 310 | | ***45*** | 18 | 400 |
| ***30*** | 18 | 600 | | | | |

Phase III Component

Participants will be randomly allocated with unequal probability, according to the specific expected cure rate by specie, to receive either:

**Treatment Arm 1**: Single dose of a tablet of ALB 400 mg (active control arm).

**Treatment Arm 2**: Single dose of a tablet of FDC 400mg-18mg or 400mg-9mg.

- For participants <45 kg of body weight at baseline: FDC of 400mg ALB-9mg IVM.
- For participants ≥45 kg of body weight at baseline: FDC of 400mg ALB-18mg IVM.

**Treatment Arm 3**: Daily dose of a tablet of FDC 400mg-18mg or 400mg-9mg for 3 days.

- For participants <45 kg of body weight at baseline: FDC of 400mg ALB-9mg IVM.
- For participants ≥45 kg of body weight at baseline: FDC of 400mg ALB-18mg IVM.

FDC will be provided as an oral dispersible formulation, while ALB will be a chewable pill. Both FDC and ALB will be taken with water after a light meal, followed by visual observation of the participant by the study physician at each site. Vomiting 1h post-treatment will require re-dosing. The participants will not

be allowed more than one repeated dose. In case that a participant vomits following re-dosing during enrolment visit, the subject will be withdrawn from the trial and standard treatment will be offered according to national guidelines. Light meal is considered as a soft breakfast with a contribution of 15 g of fat. It might be defined as 250 cc of milk with tea or coffee, 1 tablespoon full sugar (25 g) and 25 g of fat biscuits. The expected nutrient contribution is approximately 312.8 calories: 38.43 g of carbohydrates, 4.81 g of proteins and 15.5 grams of fats.

Detailed instructions for dose administration, and storage conditions will be provided to each study site.

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

### 6.2.1 ACQUISITION AND ACCOUNTABILITY

**Investigational Product Receipt and Storage at the Study Site Pharmacy**

Laboratories Liconsa shall supply adequate units of the investigational medicinal products (IMP) for administration as per protocol to each study site. On reception of the IMP at study site, each pack of IMP will be verified and ensured they are sealed and labelled correctly. The label should include: Product Name, Strength, Number of Dosage Units, Manufacturer, Lot Number or Batch Number, Expiry or Retest Date, Study Number (on test product, if available) and Storage Condition mentioned clearly.

At each study site, the designated study personnel will receive the IMP with the corresponding certificates of analysis (CoA) and will store the IMP at the required storage conditions at the study site pharmacy. An IMP accountability log will be maintained at each study site.

The FDC will be available in blister aluminium-aluminium, six tablets per blister and/or bottles per 40 counts.

The Albendazole will be supplied in bottles, 60 tablets per bottle.

**IMP Accountability**

The designated personnel at each study site, will maintain accountability of the investigational products for the trial at their corresponding site. Study drug accountability includes: the correct storage, handing, dispensing, destruction of unused IMP and maintaining records of the same for the trial.

**IMP Dispensation at site**

The investigational product will be dispensed as per the randomisation schedule. Only participants enrolled in the study will receive the IMP under the supervision of the study physician.

**Unused IMP**

All unused, partially used or completely used IMPs should be retained at each study site, till site close out. Investigational products that have not been used, will be retained in their original containers and stored appropriately. All remaining IMP will be returned by the site to Liconsa (for storage and/or destruction) after the close-out visit. Partially used, used and expired IMP will be destroyed at the site following the instructions provided by the Sponsor or returned to the Sponsor.

### 6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

**Formula ALBENDAZOLE-IVERMECTIN (400mg-9mg)**

| MATERIAL | UNITARY FORMULA | % |
|---|---|---|
| ALBENDAZOLE | 400,00 mg | 33,33% |
| IVERMECTIN | 9,00 mg | 0,75% |
| FILLER | 659,00 mg | 54,92% |
| WETTING AGENT | 18,00 mg | 1,50% |
| SWEETENER | 6,00 mg | 0,50% |
| FLAVOR | 24,00 mg | 2,00% |
| LUBRICANT | 12,00 mg | 1,00% |
| **TOTAL** | **1200,00 mg** | **100,00%** |

**Formula ALBENDAZOLE-IVERMECTIN (400mg-18mg)**

| MATERIAL | UNITARY FORMULA | % |
|---|---|---|
| ALBENDAZOLE | 400.00 mg | 33.33% |
| IVERMECTIN | 18.00 mg | 1.50% |
| FILLER | 650.00 mg | 54.17% |

| | | |
|---|---|---|
| WETTING AGENT | 18.00 mg | 1.50% |
| DISINTEGRANT | 60.00 mg | 5.00% |
| AGLUTINANT AGENT | 12.00 mg | 1.00% |
| SWEETENER | 6.00 mg | 0.50% |
| FLAVOR | 24.00 mg | 2.00% |
| LUBRICANT | 12.00 mg | 1.00% |
| **TOTAL** | **1200.00 mg** | **100%** |

**Formula RLD (Reference Listing drug (ALB))**

| MATERIAL | UNITARY FORMULA |
|---|---|
| ALBENDAZOLE | 400,00 mg |
| CORN STARCH | |
| POVIDONE | |
| SODIUM LAURIL SULFATE | |
| SODIUM CROSCARMELLOSE | |
| MICROCRYSTALLINE CELLULOSE | |
| YELLOW ORANGE S | |
| MAGNESIUM STEARATE | |
| VANILLA FLAVOR | |
| PASSION FRUIT FLAVOR | |
| ORANGE FLAVOR | |
| LACTOSE | |
| SODIUM SACCHARIN | |

**Appearance ALBENDAZOLE-IVERMECTIN (400mg-9mg):** White, oblong tablet, embossed with "9" and uncoated.

**Appearance ALBENDAZOLE-IVERMECTIN (400mg-18mg):** White, oblong tablet, embossed with "18" and uncoated.

**APPEARANCE ALB:** Pink with white points, oblong, uncoated tablet, with a score in one side and "ALB 400" in the other side.

**FDC Packaging**

Blister aluminium-aluminium per six tablets and/or bottles of 40 tablets.

**ALB packaging:** HDPE (High Density polyethylene) bottle containing 60 tablets.

**Labelling**

The labelling, blinding and packaging details of study medicine will be outlined in a separate IMP manual. The IMPs will be labelled by Laboratories Liconsa as per regulatory requirements before shipping to study sites. In addition, the labels will include: 'For Clinical Trial Use Only', Trial acronym, Storage Condition, Keep out of reach of children, Contents, Sponsor's Name and Investigator's name/ site & number. The study physician will not allow the study drugs to be used for purposes other than those indicated in this protocol.

**ALB PRODUCT MANUFACTURER**

Allen Pharmaceuticals

### 6.2.3 PRODUCT STORAGE AND STABILITY

**Storage of the IMPs (FDC and ALB)**

Store at 25ºC. Minor and transitory excursions are allowed to 15-30ºC. The product should be protect from light and humidity.

**Stability**

Proposed stability of the product will be for two years from the manufacturing date.

### 6.2.4 PREPARATION

Not Applicable. The IMPs do not need any preparation prior to administration.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

**Procedures for Randomization:** At each site, participants will be randomly allocated to one of the three treatment arms described above, after enrolment. A computer-generated randomization list will be prepared before the study start by or under the supervision of the Sponsor. Balanced allocation to the three arms in the three study sites will be ensured.

Treatment allocation for each study participant will be concealed in opaque sealed envelopes that will be opened only after enrolment. Study participants will be assigned a unique study number linked to the allocated treatment group.

Participants infected with more than one STH will be also randomized and treatment allocation will be done as for single infections. Outcomes for all infecting STH will be included in the analysis.

In addition to participant randomisation, a separate randomisation list will be generated for the study drug.
Randomization will be conducted separately for each of the three institutions recruiting participants in the clinical trial.

**Blinding**

All samples sent to the laboratory for analysis will be coded to ensure a blinded assessment of the efficacy outcomes. Participants and the study investigators assessing drug safety will not be blinded for treatment arms.

## 6.4 STUDY INTERVENTION COMPLIANCE

The study drug will be taken under direct supervision of the Site PI or delegated study physician. This will ensure study drug compliance as well as safety monitoring. The study CRF will be completed and drug intake will be noted. The drug accountability log forms will be source document used to monitor study drug compliance.

## 6.5 CONCOMITANT THERAPY

Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and supplements. Concomitant medication will be recorded throughout the study from the moment of signing of the consent form.
Antiparasitic drugs will be prohibited during the study period unless clinically indicated.
All concomitant medications taken during the study will be recorded in the appropriate sections of the CRF with indication, dose information, and dates of administration.

### 6.5.1 RESCUE MEDICINE

All participants with a positive STH infection by microscopy on the last study visit 6 (Day 21 +/- 7 days) will be provided with rescue treatment. Participants with *S. stercoralis* infection will be offered ivermectin 3mg tablets at the currently standard regimen (200µg/kg) and participants with *A. lumbricoides*, hookworms and/or *T. trichiura* will be offered albendazole through their local health centres.

In case that a participant vomits following re-dosing during enrolment visit, albendazole 400mg single dose will be administered as standard treatment when recovered.

# 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 DISCONTINUATION OF STUDY INTERVENTION

On discontinuing study intervention, remaining follow up visits and study procedures should be completed as indicated in the SOAs. If a clinically significant finding is identified after enrolment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

## 7.2 PARTICIPANT WITHDRAWAL FROM THE STUDY

Subjects who have been enrolled and, for whatever reason, discontinue the trial prematurely after randomization are classified as withdrawals. Subjects may withdraw from the trial at any time, either on their own request (withdrawal of consent/assent) or at the discretion of the investigator.

Participants are free to withdraw from participating in the study at any time.

In addition, an investigator may prematurely discontinue a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation (Screening error resulting in incorrect enrolment)
- Participant unable to receive study drug as per protocol.
- Other conditions that upon judgement of the Investigator or the DSMB, could hamper the safety of an individual and/or the validity of the study.

The reason for participant withdrawal from the study must be recorded in the subject's medical records and CRF. Participants who provide informed consent and assent forms and are randomized but do not receive the study intervention may be replaced. Participants who sign the informed consent form, and

are randomized and receive the study intervention, and subsequently withdraw consent, or are discontinued from the study, will not be replaced.

Participants who discontinue from the study will be assessed for adverse events.

### 7.3 LOST TO FOLLOW-UP

A participant will be considered lost-to-follow-up if he or she missed two study scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant is lost-to-follow-up:

- School absenteeism will be monitored and subsequent house visits will be performed for study participants missing school days during study-visit days.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost-to-follow-up.
- The measures taken to follow up must be documented in the subject's medical records.

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the CRF.

Upon withdrawal from the study, participants with documented STH infections based on the stool specimen collected in the post treatment visit, will be referred to the appropriate health care system for further evaluation, treatment, and follow-up. Reasonable attempts will be made to refer participants lost-to-follow-up to the appropriate health care system.

## 8 STUDY ASSESSMENTS AND PROCEDURES

### 8.1 EFFICACY ASSESSMENTS

**Study evaluations**

This study will consist of a screening, enrolment, treatment, post-treatment follow-up visits, illustrated in schedule visits scheme 1.4 and 1.5.

**Screening Phase**

The purpose of the screening phase is to confirm participant eligibility for enrolment in the study based on the inclusion and exclusion criteria. The objectives, procedures of the study, risks and requirements of

the study will be explained to each potential participant and to their parent/guardian or their legal representatives. Section 10.1.1.2 describes the consent procedures. Considering the context in which the clinical trial is carried out, in many cases, group meetings with the parents/guardians of the potential participants must be organized in the community before screening as part of the informed consent process. For logistical reasons the informed consent and assent process can be performed up to 3 months prior to the screening visit as part of the pre-screening activities or at the latest during the screening visit before any trial procedure is performed.

If they accept to participate in the study, the participant, parent (guardian of the participant) or legal representative will be asked to sign a written informed consent form and the participant (12 – 17 years of age) an assent form before any study-specific procedures are conducted.

The following laboratory tests will be performed at screening after written consent and assent have been obtained:

- STH diagnostic test by Kato-Katz and Baermann (stool sample): For this, the participants will be provided with a stool collection kit to provide fresh stool (collected <24h before laboratory examination). The stool sample will be tested in the laboratory as part of the eligibility criteria. On obtaining the laboratory results, participants with a positive egg count for ONLY *A. lumbricoides*, but not for other STH as per the eligibility criteria*,* will not be eligible and shall be referred to the appropriate health care system for further evaluation, follow-up, and care.
- All participants with other helminth eggs which do not fulfil eligibility criteria or those with only Ascaris will be referred to the appropriate health care system for further evaluation, follow-up and care.
- Urine pregnancy and haematuria strip test as proxy for *Schistosoma* : A urine kit will be provided in order to collect urine sample during the screening visit to test for pregnancy and to detect haematuria as a proxy for *S. haematobium* . Participants with haematuria shall be referred to the appropriate health care system for further evaluation, follow-up, and care. These participants will be included in the trial if they fulfil eligibility criteria.
- Sero-HIV test (finger prick for blood). This will only be offered for participants in Mozambique. HIV serostatus will be assessed to evaluate HIV infection as a possible covariate, due to the high

prevalence of HIV in the country but will not determine the participant's eligibility. In Kenya and Ethiopia, the low HIV prevalence does not justify HIV testing.

At each study site, a screening and enrolment log will be used to document all participants considered for enrolment regardless of whether they were enrolled or not. The screening and enrolment log will not contain names or other identifying information. A subject identification log will also be recorded to document identification of study participants enrolled in the trial in case follow-up is required. It is a CONFIDENTIAL list to be retained ONLY at the study site.

**ID assignment**

Participants who provide consent and assent will be given a screening number which will be assigned sequentially as the informed and assent forms are signed. Participants who fulfil the eligibility criteria, will be assigned with a randomisation number. Once the randomisation number is issued, the participant is enrolled and administered with study drug. The screening number will be used to identify the participant on the CRF. Once a screening number has been assigned the number cannot be reused even if the participant discontinues or is a screening failure.

**Clinical assessments**

The participant's demographic data (age, date of birth, sex, ID, parent/guardian ID, relationship, age and contact details) and all relevant clinical information as per the visit schedule including observation upon physical examination and vital signs will be recorded in the CRF.

**Baseline visit**

At baseline visit, all participants who fulfil the eligibility criteria, will be randomised to receive the assigned treatment. All participants will be observed under direct medical observation after dose administration as per each study arm. In order to facilitate trial logistics on the field during baseline visit, randomization can be performed the day before baseline visit providing that participants' arm assignment is centralized by a delegated randomization responsible.

**Treatment allocation**

Following the completion of all baseline procedures, the participants who fulfil all the eligibility criteria and who have given written informed consent will be allocated to one of the three treatment arms as described in section 4.1.

**Post-treatment Phase (Follow-Up)**

The study Site Principal Investigator (PI) or delegated study physician will observe each participant for 3h after drug administration. Safety assessment of participants will occur from day 0 (visit 1) to day 3 (visit 4). An additional safety visit will be done at day 7 (visit 5) for follow and monitoring of adverse events. On Day 21 (+/- 7 days) post treatment, a stool collection kit will be provided to each participant for stool collection to be analysed in the laboratory. All assessments for this final visit will be performed as in the SOAs. Visit 6 (Day 21 +/-7days) will be the end of study visit. All participants with a positive STH infection by microscopy on visit 6 (Day 21 +/- 7days) will be provided with rescue treatment. Participants with *S. stercoralis* will be offered ivermectin and participants with *A. lumbricoides*, hookworms and/or *T. trichiura* will be offered albendazole through their local health centres for.

**Early Withdrawal**

For participants that may discontinue or withdraw early from the study at any time before the post-treatment visit, every effort will be made to perform final assessments, as specified in the SOAs.

## 8.2 SAFETY AND OTHER ASSESSMENTS

Study procedures are specified in the SOA. The Site PI or delegated study physician will observe each participant for 3h after drug administration. A symptom-directed (targeted) physical examination will be performed at screening and when needed to evaluate possible adverse event(s) (i.e. any new symptoms). No physical exam is needed for routine study visits.

**Pharmacokinetic Assessments (Phase II component only at Kenya)**

Pharmacokinetic (PK) assessments will be conducted in participants in the three arms of the phase II trial (only Kenya). PK sampling (2 timepoints per participants in arm 1 and 2, 3 timepoints for arm 3) will be performed by finger prick using Mitra(40) Clamshell Devices. The 126 subjects included in the 3 arms of treatment will be randomly assigned to 7 subgroups (for arm 1) and 10 subgroups (for arm 2 and 3) with different sampling times (2 blood samples per subgroup) that will be extracted from all the participants.

The two sampling times are obtained from two different post-dosing ranges covering from 1 to 7 hours (range I) and from 8 to 72 hours (range II). Thus, the overall sampling times describes the entire pharmacokinetic profile for the two drugs (Ivermectine and Albendazole) for each of the 3 groups of body weight [23-<30kg, 30-45kg and 15-23kg].

PK blood sampling (2 timepoints per participant) will cover the following timepoints:

- Albendazole arm: 1, 2, 3, 4, 5, 6, 7, 8 and 24h after treatment administration.
- Single dose FDC arm: 1, 2, 3, 4, 5, 6, 7, 8, 24, 48 and 72 h after treatment administration
- Three-day FDC arm: 1, 2, 3, 4, 5, 6, 7, 8, 24, 48 and 72 h after treatment administration (time points considered respective to the last dose on day 2). For this arm, 1 additional timepoint will be collected for all participants at pre-dose Day 2.

PK data generated during the phase II component will be analysed according to the Statistical Analysis Plan.

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related. Thus, an AE is any undesirable and unintended medical occurrence in a participant including those events which do not necessarily have a causal relationship to the study drug regimen. Prior to the administration of study drug, only adverse events that meet the definition of serious (SAE (see below)) and adverse events that the Site PI or delegated study physician considers to be related to study design and/or procedures should be recorded.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases in severity level, it should be recorded as an AE.

### 8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A SAE is an AE that:

- results in death
- is a life-threatening adverse event
- requires hospitalization or prolongation of existing hospitalization

- results in a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

### 8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

The Site PI or delegated study physician is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

#### 8.3.3.1 SEVERITY OF ADVERSE EVENTS

All AEs and SAEs will be assessed for severity by direct observations of the Site PI or delegated study physician. The participant or his/her parent or guardian can also report any AEs to the study site for evaluation. The determination of the seriousness, severity, causality, and expectedness will be made by the Site PI or delegated study physician who is qualified to diagnose AE information, provide medical evaluation of AEs, and classify AEs based upon medical judgement. From the moment a study participant provides a signed informed consent and assent, the Site PI or delegated study physician will monitor each participant for the development of any clinical evidence of an AE.

The nature of the adverse event, its date and time of onset, duration and severity, therapy employed (if any) and the investigator's opinion of causality to study drug with an alternate aetiology, if appropriate, will be documented. For adverse events to be considered as intermittent or continuous, the events should be of similar nature and severity. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity. The Site PI or delegated study physician will follow up on all adverse events to satisfactory clinical resolution or the establishment of a stable chronic stage upon study completion.

The investigator will rate the severity of the adverse event according to the following definition:

Mild: The adverse event is transient and easily tolerated by the participant and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the participant's usual activities of daily living.

Moderate: The adverse event causes the participant discomfort and interrupts the participant's normal activities but poses no significant or permanent risk of harm. Events are usually alleviated with additional specific therapeutic intervention

Severe: The adverse event causes considerable interference with the participants normal activities, and may be incapacitating or life-threatening.

The study physician at each site will use the above definitions to assess the severity of the adverse event to the study drug.

#### 8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

The Site PI or delegated study physician at each site must assess the relationship between investigational product (study drug) and each AE/SAE. The study physician will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered.

The degree of certainty about causality will be graded using the categories below.

Definite: The adverse event has a strong temporal relationship to study drug and/or recurs on re-challenge, and cannot be explained by an alternative aetiology.

Probably: The adverse event has a strong temporal relationship to study drug or recurs on re-challenge, and an alternative aetiology is unlikely or significantly less likely.

Possibly: The adverse event has a strong temporal relationship to the study drug, and an alternative aetiology is equally or less likely compared to the potential relationship to study drug. The alternate aetiology should be provided by the investigator.

Unlikely: The adverse event has little or no temporal relationship to the study drug and/or a more likely alternative aetiology exists. The alternate aetiology should be provided by the investigator.

Unrelated: The adverse event is due to underlying or concurrent illness or effect of another drug and is not related to the study drug. The alternate aetiology should be provided by the investigator.

The categories “unrelated” and “unlikely” will be mapped to “unrelated”, the categories “possible”, “probable” and “definite” will be mapped to “related”.

#### 8.3.3.3 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS)

The Site PI or delegated study physician will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. Such adverse events are called SUSARS. That is any SAE where a causal relationship with the study drug is at least reasonably possible but is not listed in the reference safety information section of the investigators brochure (IB).

### 8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant during a study visit, or upon review by the study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured in the CRF. Information to be collected includes event description, time of onset, the study physician’s assessment of severity, relationship to study drug, and time of resolution/stabilization of the event. All AEs that occur

during the study duration must be documented appropriately regardless of the relationship. All AEs will be monitored to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented on the source documents to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

### 8.3.5 ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

All AEs that meet the definition of SAE will be reported to the Sponsor by the Site PI or delegated study physician or an assigned representative within 24 hours of the site becoming aware of it, using a study SAE form located in the Investigators Folder (IF), which should be completed, scanned and sent via email to the Sponsor.

ISGlobal

C/Rosselló 132

Barcelona 08036, Spain

SAE Email Address: ALIVE.Pharmacovigilance@isglobal.org

The SAE form should include nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. probably, possibly, unlikely, unrelated). The delegated study physician should assign the causality of the event.

### 8.3.6 REGULATORY REPORTING OF SAES

SAE reporting by each site, will comply with local regulations for SAE reporting to the sites EC/IRB and regulatory authorities.

All unexpected SAEs must be reported to the ethics committee within 15 days (7 days in case of death) from knowing of the SAE. In addition to the expedite SAE reporting in 24h, monthly aggregate and annual reports will be written by the Site PI or delegated study physician at each site.

A copy of the final study report will be provided to the regulatory authorities for each country and the DSMB.

In addition, ISGlobal will report all SAEs to the DSMB as well as the CEIm (EC for ISGlobal). ISGlobal will also report any SUSAR to EudraVigilance (EU) and will notify all the study site PIs as soon as possible.

### 8.3.7 PREGNANCY

Participants who are ≥12 years old (or post menarche) must have a negative urine pregnancy test to be enrolled into the study. No further pregnancy test will be performed. The duration of the study is 21 (+/- 7days). Female participants ≥12 years old will be advised against pregnancy.

In the unlikely event of pregnancy during the trial, pregnancy must be reported to the Sponsor Pharmacovigilance team (ALIVE.Pharmacovigilance@isglobal.org) by the Site PI or delegated study physician within 24 hours of the site becoming aware of it, using a study Pregnancy notification form located in the Investigator's Folder. The investigator must follow up on pregnancies discovered after IP administration until delivery and document the outcome on a new *Pregnancy notification form,* clearly marked as follow-up report. The event fulfils the criterion for an SAE in case of a congenital anomaly (birth defect), foetus death or spontaneous abortion, or adverse events in the neonate that are classified as serious.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 STATISTICAL HYPOTHESES

The main hypothesis is that FDC (either at single or 3-day regimens) will be more effective against STH than the current strategy (single dose ALB alone).

Specific hypotheses:

- Primary Efficacy Endpoint: Higher estimated CR for *T. trichiura* 21 days after treatment using microscopy in participants allocated to arms 2 and 3 than to arm 1.
- Secondary Efficacy Endpoint(s):
    - Higher estimated CR for hookworm and *S. stercoralis* 21 days after treatment using microscopy in participants allocated to arms 2 and 3 than to arm 1.
    - Higher estimated ERR for hookworm, *T. trichiura* and *S. stercoralis* 21 days after treatment using microscopy in participants allocated to arms 2 and 3 than to arm 1
    - Higher estimated CR for hookworm, *T. trichiura* and *S. stercoralis* 21 days after treatment using PCR in participants allocated to arms 2 and 3 than to arm 1.

## 9.2 SAMPLE SIZE

Sample size was calculated based on available data from peer-review publications complemented with reasonable estimates of efficacy for those experimental groups that have not been previously tested. Given the public health relevance of generating data for each species of STH of interest to this trial, sample size calculations are made to provide adequate power for each of these species, including that in the primary endpoint (*T. trichiura*) and those in the secondary endpoints (hookworms and *S. stercoralis*). For these calculations, the efficacy of the control arm (Albendazole 400mg in a single dose), was obtained for *T. trichiura* and hookworms from a systematic review and meta-analysis where temporary trends in efficacy (with the corresponding confidence intervals) were incorporated (Table 3)(4). For the efficacy of the control arm against *S. stercoralis*, an alternative source was used since the systematic review by *Moser* (54) *et al* did not include this species; for that reason, a clinical trial that included an arm of Albendazole 400mg for 3 consecutive days was used, assuming a “best case scenario” for the efficacy of the control group; this estimated efficacy is also in the range of a systematic review assessing the efficacy of Albendazole at various (but not single) doses (54). For the FDC at single dose, the calculations were based

on the estimated efficacies (and their corresponding confidence intervals) in a systematic review that calculated the Relative Risks of cure of diverse drug regimens against Albendazole 400mg single dose (Table 3)(30,55). For. *S. stercoralis*, the estimated efficacy of FDC was calculated based on a recent clinical trial using Ivermectin single and multiple-dose regimens(56). Finally, for the FDC in 3-dose regimens, considering its use in public health, deployment logistics in MDA campaigns and expected impact of the FDC, we estimated that an improvement of at least 15 percentage points would be the minimum improvement in efficacy to be demonstrated in order to make the FDCx3 regimen worth considering.

Sample size was calculated estimating the efficacy of the different experimental drug or combinations for each of the STH of interest (57,58), and gathering the individual samples sizes for the study. The sample size was calculated for pairwise comparisons of the expected Cure Rates for three study groups with an overall significance level of 5% adjusted for multiple tests by Bonferroni's correction, 80% power and inflated for 10% lost-to-follow-up.

The estimated total number of participants for the adaptive design is 1223 (*T. trichiura* 625, *S. stercoralis* 286 and hookworm 312). This sample size is powered to be able to measure efficacy for all three species in the phase III component. The sample size for the phase II component is 20% of the total participants for *T. trichiura* (126 participants). The remaining 80% of the *T. trichiura* participants will be randomised in the phase III component. Table 2 details the stratification of the participants per species with a 10% lost-to-follow-up.

The total number of participants to be included in this clinical trial is 1223 (126 in phase II and 1097 in phase III). Following randomisation, 251 participants will be allocated to the ALB treatment arm, 427 will be allocated to the FDC treatment arm and 419 in the FDCx3 treatment arm. Table 2 details the stratification of the participants per species with a 10% lost-to-follow-up.

The 10% lost-to-follow-up inflated sample sizes of the ALB-group for *T. trichiura*, *S. stercoralis* and hookworm are 129, 47 and 101 respectively, and the corresponding sample sizes of the individual experimental treatment groups are 248, 120, and 101 for FDC-group and 248, 119 and 110 for FDCx3-group. The corresponding powers of each of the tests are 91%, 100% and 80% to compare the CRs of *T. trichiura* in ALB *vs* FDC, ALB *vs* FDCx3 and FDC *vs* FDCx3 respectively; 95%, 100% and 80% to compare the

CRs of *S. stercoralis* in the above-mentioned comparisons and 82%, and 80% to compare the CRs of hookworm respectively for ALB vs FDCx3 and FDC vs FDCx3 comparisons. We do not compare CRs of hookworm in ALB and FDC as they are known to be the same. These powers were computed assuming that the expected CRs for *T. trichiura* are 23.7%, 43.7% and 59% in the ALB, FDC and FDCx3 groups respectively; 45%, 79% and 94% for *S. stercoralis* and 79.5%, 79.5% and 95% for hookworm. **Table 1** and **Table 2** show the sample size calculation according to the expected Cure Rate for each drug and helminth of interest, and the resulting sample size inflated by 10% due to the estimated lost-to-follow-up. Assumptions used for the sample size calculations (e.g. expected CRs, lost-to-follow-up, etc) should be checked during the interim analysis.

**Table 1. Sample size and power calculation according to the expected efficacy (Cure Rate) of the different treatment arms**

| Comparison | Target Power | Actual Power | Sample Size | Expected Cure Rate | Overall Alpha | Bonferroni adjusted Alpha |
|---|---|---|---|---|---|---|
| *Trichuris trichiura* | | | | | | |
| ALB | | | 116 | 23.7% | | |
| vs IVM-ALB | 80% | 91% | 223 | 43.7% | 0.05 | 0.0167 |
| vs (IVM-ALB)x3 | 80% | 100% | 223 | 59% | 0.05 | 0.0167 |
| IVM-ALB vs (IVM-ALB)x3 | 80% | 80% | | | 0.05 | 0.0167 |
| *Strongyloides stercoralis* | | | | | | |
| ALB | | | 42 | 45% | | |
| vs IVM-ALB | 80% | 95% | 108 | 79% | 0.05 | 0.0167 |
| vs (IVM-ALB)x3 | 80% | 100% | 107 | 94% | 0.05 | 0.0167 |
| IVM-ALB vs (IVM-ALB)x3 | 80% | 80% | | | 0.05 | 0.0167 |
| Hookworm | | | | | | |
| ALB | | | 91 | 79.5% | | |
| vs IVM-ALB | 80% | -- | 91 | 79.5% | 0.05 | 0.0167 |
| vs (IVM-ALB)x3 | 80% | 82% | 99 | 95% | 0.05 | 0.0167 |
| IVM-ALB vs (IVM-ALB)x3 | 80% | 80% | | | 0.05 | 0.0167 |

**Table 2. Final sample size calculation taking into account 10% lost-to-follow-up**

| | Phase II | | PHASE III | | PHASE II/III |
|---|---|---|---|---|---|
| **Group** | N | N total Phase II[1] | N | N total Phase III[1] | **N total** |
| ***Trichuris trichiura*** | | | | | |
| ALB | 23 | **26** | 93 | **103** | **129** |
| FDCx1 | 45 | **50** | 178 | **198** | **248** |
| FDCx3 | 45 | **50** | 178 | **198** | **248** |
| **Total** | **113** | **126** | **449** | **499** | **625** |
| ***Strongyloides. stercoralis*** | | | | | |
| ALB | | | 42 | **47** | **47** |
| FDCx1 | | | 108 | **120** | **120** |
| FDCx3 | | | 107 | **119** | **119** |
| **Total** | | **0** | **257** | **286** | **286** |
| **Hookworm** | | | | | |
| ALB | | | 91 | **101** | **101** |
| FDCx1 | | | 91 | **101** | **101** |
| FDCx3 | | | 99 | **110** | **110** |
| **Total** | | **0** | **281** | **312** | **312** |
| **TOTAL** | | **126** | | **1097** | **1223** |

[1]Calculated by inflating the sample size using considering 10% lost-to-follow-up

## 9.3 ANALYSES POPULATIONS

- Intention-to-Treat (ITT) population: defined as all randomized participants with valid informed consent.
- Modified Intention-to-Treat population: defined as all participants who took at least one dose of study intervention and/or have some particular amount of follow-up outcome data.
- Safety population: defined as the subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of study intervention).

- Per-Protocol population: defined as a subset of the participants in the full analysis (ITT) set where participants with major protocol deviations will be excluded.
- Sensitivity analysis populations (if needed)

## 9.4 DATA MANAGEMENT

Each trial site will be responsible for the internal quality management of study conduct, data and biological specimen collection, documentation and accurate CRF completion. A data management plan will be developed for each site. Any change the site-specific data management plan will be reported to the Sponsor.

Participant data will be collected using electronic CRF. Laboratory results will be recorded in adhoc database at each site. All data storage will be encrypted and password protected.

A Data Transfer Agreement will be established between the Sponsor and Study sites.

## 9.5 STATISTICAL ANALYSES

### 9.5.1 GENERAL APPROACH

A Statistical Analysis Plan (SAP) for the trial will be developed. Two interim efficacy analyses are planned: 1) after the end of the phase II component for decision making to move to the phase III component; 2) after 50% of the study participants are enrolled. Regular evaluation of the safety data every 3 months will be performed by the DSMB. The study is designed as a superiority trial, so all tests will be two-sided and all statistical significance will be declared at the 0.05 level. Analysis will be done using R.

### 9.5.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary safety endpoints in phase II, are the frequency, type, severity and relationship to study drug for all adverse events and severe adverse events.

The primary efficacy endpoints for the efficacy phase III trial the cure rates for *T. trichiura* and 21 days after treatment using microscopy. Cochran–Mantel–Haenszel (CMH) test, controlling the effect of site if that is appropriate (sufficient participants), will be used to compare the cure rates for the 3 treatment

groups. A participant is considered cured if the baseline egg count or larval count is not 0 while the post-treatment egg count or larval count is 0.

A total of 2 stool samples (1 pre-treatment and 1 post-treatment) will be obtained from each participant. The primary efficacy analysis will be based on ITT population. Efficacy for each type of infection will be analysed separately. A participant with multiple infections will be included in the analysis of each target species that the participant is infected with.

Stool sample collected pre-treatment will be used for the baseline information, and stool sample collected post-treatment will be used for the post-treatment information in the statistical analysis.

**Pharmacokinetic parameters**

FDC concentrations (Cmax), time to reach Cmax (Tmax) and area under the curve (AUC). For the pharmacokinetic analysis, PK parameters will be obtained by non-compartmental analysis using WinNonlin (5.2, Certara, Princeton, NJ, USA). Maximum FDC concentrations (Cmax) and time to reach Cmax (Tmax) will be observed values. The half-life (the time in which half of the absorbed drug is eliminated) will be calculated as t1/2"ln(2)/kZ. AUC was determined until the last measurement (AUC0–72) and until infinity (AUCINF).

**Palatability/Acceptability**

Acceptability assessment will be made after the administration of the last dose in each group. For the single dose posology group, the assessment will be done after the administration but for the three-days posology group assessment will be made after the third dose only. Compliance/adherence to drug treatment will be also recorded during the trial. The primary attributes for an orodispersible formulation to be measured are taste, smell, texture and time needed to dissolve/disperse (duration of administration). Also, the attributes will be measured as follows:

**Table 3. Numerical rating scales (NRSs) for palatability/acceptability assessments of parents and caregivers oral use formulations**

| Score | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Overall opinion of taste | Very bad | Bad | Acceptable / OK / Not nice and not bad | Good / Nice | Very good / Very nice |
| Overall opinion of smell | Very bad | Bad | Acceptable / OK / Not nice and not bad | Good / Nice | Very good / Very nice |
| Overall opinion of texture | Very bad | Bad | Acceptable / OK / Not nice and not bad | Good / Nice | Very good / Very nice |

Parents and caregivers will be also asked for their assessment of the acceptability. The scale for parents is shown in Table 4 and will be a NRS scale with associated phrases about their opinion of their child's acceptability.

**Table 4. Numerical rating scales (NRSs) for palatability/acceptability assessments of parents and caregivers oral use formulations**

| Score | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Parent or caregivers overall opinion on their child's acceptability of the formulation[4] | Very bad | Bad | Acceptable / OK | Good | Very good |

The questions that will be asked to the participants are:

1. Could you please let us know your opinion of the taste of the medicine you just had?
2. Could you please let us know your opinion of the smell of the medicine you just had?
3. Could you please let us know your opinion of the texture (feel) of the medicine you just had?

The question that will be asked to the parent/caregiver is:

1. Could you please let us know your opinion that best describes the child's acceptability of the formulation?

### 9.5.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Egg count reduction for each species (for *hookworms*) at end of treatment period will be estimated. *S. stercoralis* will not be evaluated by this analysis.

Percent egg count reduction is defined as:

$$\frac{\text{(egg count at pre-treatment – egg count at post-treatment)}}{\text{egg count at pre-treatment}} \text{ x100\%}$$

For the statistical analysis, a logarithmic transformation will be conducted. As there may be participants with a count of zero eggs in the post-treatment stool sample, a value of 1 will be added to total egg count at baseline and total egg count at post-treatment so that the logarithmic transformation can be applied. The geometric mean will be used to summarize the mean egg count at pre-treatment and post-treatment visits and in the calculation of the mean percent egg reduction. Treatment differences will be evaluated by an analysis of covariance (ANCOVA), in which the logarithm of the egg count at post-treatment is the dependent variable, site (if appropriate), and treatment as fixed effect, and the logarithm of the egg count at pre-treatment is the covariate. Baseline egg count will also be analysed as an independent variable that conditions treatment response (60).

Correlation between Kato-Katz counts and PCR will be explored through linear regression tests of Pearson´s or Spearman´s (according to the underlying distribution). Kappa test will be used for the evaluation of both tests in the calculation of CR.
Relevant covariates will also be included in the data analysis. Particularly, HIV infection will be assessed as a covariate in participants recruited in Mozambique.

For the resistance testing, significant associations between the presence of resistance mutations and treatment arm will be explored through stratified bivariate analysis and afterwards, adjusted through multivariate logistic regression models; statistical significance will be assessed by Chi-square test with 95% significance. Baseline counts (for hookworm and *T. trichiura*) and site of enrolment will be assessed as covariates.

### 9.5.4 SAFETY ANALYSES

For the safety analysis in phase III, the ITT (those participants who have received at least one dose of study intervention) will be used for the analysis and participants will be considered by arm and by both FDC arms pooled (overall) and by number of doses of FDC received to explore dose-responses. Drug-related AEs will be analysed using ordinal logistic regression with the untoward effect classified as absent, mild,

moderate, or severe and the factorial treatment regimens (without interaction term) as predictor variables. For a count outcome such as the number of AEs or SAEs incidence rate ratio (IRR) and its 95% CI will be computed using Poisson or Negative binomial regression.

### 9.5.5 ADHERENCE ANALYSIS

Adherence analysis will be done in order to capture the reason for withdrawal or discontinuation, as this may be helpful for future studies and/or this may impact the final results.

### 9.5.6 EXPLORATORY ANALYSES

Exploratory analysis will be performed to try to understand the potentially large number of unknown confounders/effect modifiers in this study.

### 9.5.7 SUB-GROUP ANALYSES

Subgroup analyses will be performed for the primary outcome on the ITT population. The variables for for the subgroup analysis will include:

Drug exposure: categorized by >400 µg/Kg vs ≤400 µg/Kg

Age: categorized by SAC (5 to 14 years-old) & young adults (15 to 18 years-old).

Co-infection: categorized by mono-infected vs co-infected

Worm burden: categorized by WHO categories of egg burden categories measured by Eggs Per Gram (EPG) through Kato-Katz method (1):

| Species | Light | Moderate | Heavy |
|---|---|---|---|
| *T. trichiura* | 1 – 999 | 1000 – 9999 | ≥10000 |
| Hookworms | 1 – 1999 | 2000 – 3999 | ≥4000 |

### 9.5.8 MISSING DATA

Every effort will be made to minimise the amount of missing data in the trial. Information on the reason for missing data will be obtained, whenever possible. Multiple imputation analysis will be performed if needed.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

This study will be conducted in conformity with the principles set forth in the Declaration of Helsinki in its current version; the requirements of Good Clinical Practice (GCP) as defined in Guidelines and The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice; and all national and local regulations and guidance applicable at each site.

Each institution engaged in this research will hold registered IRBs/ECs that will review and approve this protocol, associated informed consent documents, recruitment material, and handouts or surveys intended for the participants, prior to the recruitment, screening, and enrolment of participants. The IRB/IEC review shall be in accordance with ICH E6 (R2), and other regulations and policies, as applicable.

Site IRBs/IECs may have additional national and local regulations.

Any amendments to the protocol or consent materials will be approved by the IRB/EC before they are implemented. IRB/EC review and approval will occur at least annually throughout the duration of the study. The Site PI will notify the IRB/IEC of deviations from the protocol and SAEs, as applicable to the IRB/EC policy.

### 10.1.1 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Investigators or designated research staff will obtain a participant's informed consent in accordance with the requirements of national and local regulations and policy, and ICH E6 GCP before any study procedures or data collection are performed.

Participants and their legal representatives/guardians will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The key information about the study will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

ICFs will be IRB/EC-approved, and participants will be asked to read and review the consent form. Participants and legal representatives/guardians must sign the ICF prior to starting any study procedures

for this trial. Once signed, an original copy of the ICF will be given to the participant for their records and an original copy will be kept in the site investigators folder.

New information will be communicated by the site PI or delegated personnel to the participants who consent to participate in this trial in accordance with IRB/EC requirements. The informed consent document will be updated, and participants will be re-consented per IRB/EC requirements, if necessary.

#### 10.1.1.1 CONSENT AND ASSENT DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. Written informed consent and assent will be in the local language.

#### 10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Prior to the onset of the study, community meetings will be held in all village's catchment area of the schools to describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Information sheets will be provided during the meeting for their review.

At school-level individual-level parental informed consent will be sought. If a participant, parent, guardian or older child is unable to read or write, his/her fingerprint will be used in substitute for a signature, and a signature from an impartial witness to the informed consent discussion will be obtained.

Participants, parents and guardians will have the chance to ask questions and will be informed that their participation and that of their child(ren) in the study is completely voluntary and that they may withdraw from the study at any time. Information about all participants, including age, gender, and any history of known allergies or adverse reactions to study medications, will be obtained and captured on an initial screening form. Assent to participate in the trial will be obtained from children 12-17 years.

Verbal assent to participate in the study will also be obtained from the child at the time of parasitological surveys.

*Community engagement*

Prior to the onset of the study, meetings will also be held with officials from the District Education Office, the District Health Management Team and the County Office to sensitize them about the study and plans for recruitment and follow-up. Similar meeting will also be held with health and education officials at the national level in in each country.

*Benefits*

The most immediate benefit of the study is free medical treatment for helminth infections.

*Risks*

Stool and urine sample collection may be embarrassing for the children, but this discomfort will be minimized by guaranteeing children's privacy during stool collection.

*Insurance*

The sponsor will take out trial insurance such that participants enrolled into the study are covered by indemnity for non-negligent harm associated with the protocol.

### 10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause to do so. Written notification, documenting the reason for study suspension or termination, will be provided to study participants, study physician, funding agency and regulatory authorities. If the study is prematurely terminated or suspended, the study physician will promptly inform study participants, the IRB/EC and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed and approved by the regulatory authorities.

### 10.1.3 CONFIDENTIALITY AND PRIVACY

All records will be kept as confidential as possible. Participants will be identified primarily by their screening number; names will not be entered into the computerized database. No individual identities will be used in any reports or publications resulting from the study.

No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB,or EC regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the site.

The study participant's contact information will be securely stored at each trial site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB or EC, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at ISGlobal. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by trial sites and by ISGlobal research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at ISGlobal.

### 10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be centralised at ISGlobal and analysed by the STOP consortium. Stored specimens (stool and larvae) will be stored at each trial site according to the study SOP for sample collection and storage. All samples will be stored for up to a maximum period of 10 years or until laboratory testing are completed.

Stool samples will be shipped between the three trial sites for quality control purposes by PCR to confirm microscopic results from Kato-Katz and Baermann test. Should technical issues arise or in case of discrepancy in results, an aliquot of the stool sample will be shipped to LUMC in the Netherlands for QC purposes. Some samples will also be shipped to other research laboratories for resistance studies.

All specimens will not have any data that can be used to trace the study participant.

### 10.1.5 SAFETY OVERSIGHT

Safety oversight will be under the direction of ISGlobal and a DSMB composed of individuals with the appropriate expertise. The members of the DSMB are independent from the study conduct and free of conflict of interest. The DSMB will contact at least once a month to assess safety and efficacy data of each arm of the trial. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined.

The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety as well as study conduct and progress, including efficacy, and 2) provide clearance during the phase II component to proceed enrolment through the different weight groups and to initiate the phase III component 3) to make recommendations to the investigators concerning the continuation, modification, or termination of the trial. The DSMB will consider study-specific data as well as relevant background knowledge STH, study drugs and the population under study.

Members of the DSMB will include 3 independent members with expertise in the study drugs and STH. Reports to the DSMB will be performed by the trial statistician and will have an independent statistician upon request. Meetings and communications from the DSMB will require the participation of all 3 members.

### 10.1.6 CLINICAL MONITORING

Clinical site monitoring will be conducted ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirements.

Monitoring will be performed by a clinical monitor appointed by the Sponsor. A monitoring plan will be developed.

During the study, the monitor will have regular site contacts, including conducting on-site visits to:

- Confirm that the study is being performed according to the protocol, ICH GCP and applicable regulations, data are being accurately recorded in the CRF and that investigational product accountability is being performed.

- Conduct source data verification.
- Confirm facilities remain acceptable.
- Provide information and support to the investigators.
- Evaluate study progress.

Upon completion of the study the monitor will visit the study site to verify that all CRFs are completed and collected, all data queries have been resolved and filed, conduct final accountability, reconciliation and arrangements for investigational product and verify all study site records are complete.

The Site PI and delegated study physician and delegated site personnel will be available at monitoring visits and agree to allocate sufficient time to the monitor to discuss any issues and address their resolution.

### 10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Each trial site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

**Quality control of laboratory tests**

Regular audits of laboratory performance will be completed by experienced supervisors according to standard operating procedures. All laboratory staff will also participate in slide reading proficiency tests as part of external quality assurance and only expert microscopist will read the stool slides.

Quality control system will be implemented for all the laboratory procedures, which will include on-site trainings, design of training materials and strategies for the control of microscopy based and molecular biology tests. As part of the procedures already designed, PCR will be performed at the end of recruitment of all the study participants.

### 10.1.8 DATA HANDLING AND RECORD KEEPING

#### 10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the study personnel at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the eCRF. The data system will include password protection and internal quality checks. Clinical data will be entered from the source documents and no direct data entry in the eCRF will be performed.

#### 10.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable.

#### 10.1.8.3 SOURCE DATA

Source data are all information in original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP, regulatory, and institutional requirements. Data recorded in the CRF derived from source documents should be consistent with the data recorded on the source documents.

### 10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or International Conference on Harmonisation Good Clinical Practice (ICH GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations as soon as possible. All deviations must be addressed in study source documents and reported to the Sponsor. The study personnel are responsible for knowing and adhering to the reviewing regulatory requirements.

### 10.1.10 PUBLICATION

This study will be conducted in accordance with publication and data sharing policies and regulations. Following completion of the study, results of this research will be published in scientific journal(s) as well as to the general public in meetings or in conferences. A publication policy will be drafted for the purpose of the consortium.

The investigators will ensure that all study personnel including the study physicians involved in the study will respect the confidentiality of any information about the participants of the trial.

## 10.2 ADDITIONAL CONSIDERATIONS

**Trial site selection**

All three sites offer a combination of expertise, complementary prevalence of the three species of STH under study and laboratory facilities to conduct studies of this type:

Bahir Dar University, Amhara, Ethiopia: this site has been able to identify high prevalence of infections with hookworms and *S. stercoralis* in their area of influence and has been leading clinical research on the topic (61).

KEMRI, Nairobi, Kenya is the reference institution in the country with long-standing experience and expertise in STH and a key role in mapping the distribution of these infections; high prevalence of hookworms and *T. trichiura* have been detected in the study area as part of ongoing studies (62–64).

FM-CISM, Manhiça, Mozambique: The last national survey of STH distribution in Mozambique was conducted in 2008, showing a 53.5% prevalence for STH (65). The estimated prevalence of STH in Maputo Province where the clinical trial will be conducted was 37.1% and the prevalence of *T. trichiura* was 45%. Preliminary data from a pilot study conducted in Manhiça showed 8% prevalence of S*. stercoralis* in the study area (Muñoz, unpublished data).

## 10.3 ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| ALB | Albendazole |
| ATP | According-To-Protocol |
| CoA | Certificate of Analysis |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| DSMB | Data Safety Management Board |
| eCRF | Electronic Case Report Forms |
| EDCTP | European and Developing Countries Clinical Trials Partnership |
| EMA | European Medicines Agency |
| ERR | Egg Reduction Rate |
| FDC | Fixed Dose Co-formulation |
| GBD | Global Burden of Disease |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practices |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| IMP | Investigational Medicinal Product |
| IF | Investigators Folder |
| ITT | Intention-To-Treat |
| IVM | Ivermectin |
| NTDs | Neglected Tropical Diseases |
| PC | Preventive Chemotherapy |
| PCR | Polymerase Chain Reaction (real-time) |
| PI | Principal Investigator |
| PSAC | Pre-School Age Children |
| QA | Quality Assurance |
| QC | Quality Control |
| SOA | Schedule Of Activities |
| SAC | School-Age Children |
| SAE | Serious Adverse Event |
| SOP | Standard Operating Procedure |
| STH | Soil Transmitted Helminths |
| SUSAR | Suspected unexpected serious adverse reactions |
| WHO | World Health Organisation |
| YLD | Years lived with disability |

## 10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of regulatory approved versions of the protocol, including a description of the change and rationale.

| Version | Date | Description of Change |
|---|---|---|
| v1.4 | 20th February 2019 | **Original**<br>(based on the clinical trial proposal submitted to the EDCTP on the 31st of October 2017 for grant approval) |
| V2.1 | 20th May 2020 | Changes of the trial design from a phase III to an adaptive phase II/III clinical trial. Thus, the safety and pharmacokinetics of the FDC is tested in the phase II component prior to testing its efficacy in the phase III component of the trial. The primary endpoint of the phase III component will now be CR for *T. trichiura.*<br>General typos and administrative corrections. |
| V3.0 | 25th August 2021 | Phase II component<br>• A description of the procedures for staged enrolment and DSMB clearance has been included. Recruitment will start with the weight group 1 and only after safety data has been reviewed by the DSMB and clearance provided recruitment in the following weight group will be initiated.<br>• Secondary objective and endpoints updated to include efficacy of FDC in paediatric population.<br>• PK section updated to include population PK. Two sampling times per participant included covering two different post-dosing ranges from 1 to 7 hours post-administration and from 8 to 72 hours post-administration. The overall sampling times describe the entire pharmacokinetic profile for the two drugs (IVM and ALB) for each of the 3 groups of body weight [23-<30kg, 30-45kg and 15-23kg].<br>Phase II- Phase III component<br>• Stopping rules have been clarified. Rules for dose escalation in phase II and for the progression from phase II to phase III have been included as well as stopping rules for further dosing and trial termination.<br>• Rescue medication section updated.<br>• Guidance provided to the site concerning potentially interacting drugs: current use of warfarin at screening has been included exclusion criteria.<br>• The Schedule of Activities has been updated to include the possibility of unscheduled visits. |

| | | |
|---|---|---|
| | | • Pregnancy reporting requirements have been included.<br>• IMP storage requirements have been updated.<br>• Study monitor contact details updated.<br>• General typos and minor inconsistencies corrected. |
| V4.0 | 21st January 2022 | • Schedule of Assessments adjusted to reflect that haematuria strip test is done for Schistosoma, no measurement of weight/height is required at withdrawal visit, pre-screening activities starting 3 months prior to screening, acceptability in phase II only applies for FDC arms.<br>• Typographical error adjusted in the PK section: FDCx3 arm has an additional PK time pre-dose Day 2 (instead of Day 3), before the last intake of the study medication.<br>• Section 9 Statistical considerations updated to adjust an inconsistency in the treatment arms.<br>• Consent process allowed to be performed up to 3 months prior to screening.<br>• Randomization envelopes allowed to be opened by responsible on the day prior to baseline visit. |

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