Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	An open-label, Phase III efficacy and safety study of L-praziquantel orodispersible tablets (L-PZQ ODT) in Schistosoma-infected children 3 months to 6 years of age, including a 2:1 randomized, controlled cohort of Schistosoma mansoni-infected children 4 to 6 years of age treated with L-PZQ ODT or commercial PZQ (Biltricide®)
Study Number:	MS200661-0003
Amendment Number	2
Merck Compound Number:	MSC2499550A
Short Title:	Phase III pediatric study with the L-PZQ ODTs
Coordinating Principal Investigator (Ivory Coast): **Local Principal Investigator and Medical Responsible (Ivory Coast):** **Principal Investigator (Kenya):**	PPD PPD PPD
Sponsor Name and Legal Registered Address:	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany Medical Responsible: Name: PPD Address: Frankfurter Strasse 250 64293 Darmstadt, Germany Phone : PPD E-mail : PPD

Regulatory Agency Identifying Numbers:	PACTR 201810634034543 Clinical Trials.gov: NCT03845140
Protocol Version:	1.2
Replaces Version:	1.1 / 20 February 2019 (Kenya) 1.1 / 19 March 2019 (Ivory Coast)
Approval Date:	11 August 2020
Medical Monitor Name and Contact Information:	PPD [redacted]

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	24 Oct 2018
1.1 Kenya 1.1 Ivory Coast	Amended Protocol Amended Protocol	20 Feb 2019 19 March 2019
1.2	Amended Protocol	11 August 2020

Protocol Version 1.2 (11 August 2020)

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The rationale for the protocol amendment is as follows:

- To include an additional follow-up visit
- To update the Sponsor medical responsible
- To assess the serum concentration of up to 15 subjects in Cohort 1b and up to 15 additional subjects in Cohort 4
- To clarify the exploration of metabolites in plasma samples
- To update the urine sampling allowing for additional sampling at Week 5 post dose for Cohort 4 subjects to be treated at 60 mg/kg

Section # and Name	Description of Change	Brief Rationale
Title Page	Update the name and contact details of the Sponsor medical responsible and addition of both Principal Investigators (PIs) details for Ivory Coast	The medical responsible was changed in the study and to mention both PIs as requested by Ethics committee in Ivory Coast
Section 1.1 Synopsis: Objectives and Endpoints Table - Secondary Objectives	The definition for clinical cure was updated. Text was added regarding additional urine samples for testing, and additional Extended Follow-up visits	Text was added to the clinical cure rate to include the Extended Follow-up visits to identify cure rates beyond Week 3.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Addition of an Extended Follow-up visit (Day 35 to 40)	The table was updated to allow for the Extended Follow-up visit.
Section 3 Table 1 Objectives and Endpoints - Secondary Objectives	Addition of Extended Follow-up visit information and clarification of clinical cure definition	Text was added to the clinical cure rate to include the Extended Follow-up visits to identify cure rates beyond Week 3.
Section 4.1 Overall Design	Addition of the Day 35 to 40 Extended Follow-up visit	To align protocol text with addition of the Extended Follow-up visit (Day 35 to 40)
Section 4.2.5 Endpoints	Addition of the Day 35 to 40 Extended Follow-up visit, and the addition of PK sampling in the Biltricide control arm	Alignment of text related to the addition of the Extended Follow-up visit (Day 35 to 40), and inclusion of PK sampling in the Biltricide control arm
Section 4.4 End of Study Definition	End of study definition was updated to include the Extended Follow-up visit	Alignment of text regarding end of study due to addition of the Extended Follow-up visit for Cohort 4
Section 5.2 Exclusion Criteria	Alignment of exclusion criteria between the Kenya and Ivory Coast protocols by removing the following exclusion criteria listed in the Ivory Coast protocol: • Marked increases of the liver enzymes: alanine aminotransferase and/or aspartate aminotransferase above 3 times the upper limit of normal (ULN); total bilirubin level above 1.5 times the ULN • Participants with hepatosplenic schistosomiasis	Harmonization of the Kenya and Ivory Coast protocols

Section # and Name	Description of Change	Brief Rationale
Section 5.4 Screen Failures	Clarification of the handling of participants not eligible for enrollment due to a temporary exclusion criterion. Addition of text regarding blood sampling volume restrictions	The text was added due to a request from the Pharmacy and Poisons Board of Kenya.
Section 6.5.1 Rescue Medicine	The word "schistosomiasis" was added to explicitly state the infection type	Text added for clarification
Section 8 Study Assessment and Procedures, Follow-up visits	Addition of the Extended Follow-up visit (Day 35 to 40) The Rapid Diagnostic Test (RDT) may now be performed at the discretion of the Investigator for Ivory Coast sites.	Alignment of text regarding end of study due to addition of the Extended Follow-up visit. Harmonization of the Kenya and Ivory Coast protocols
Section 8.5 Pharmacokinetics	Update the number of subjects with PK sampling to a total of 30 for the haematobium arm (Cohort 4) Include PK sampling for up to 15 subjects in Group 1b (Biltricide).	The text was modified to address the PK sampling after a dose increase to 60 mg/kg for the Haematobium arm. The text was modified due to the inclusion of PK sampling in the Biltricide control arm
Section 9.4.4	Addition of an interim analysis without pausing the study was to be performed after 30 participants in Cohort 4 were treated at 60 mg/kg.	The purpose is to inform other studies within the Sponsor's clinical program.
Appendix 4	Addition of Extended Follow-up visit sampling requirements	To document the study sampling requirements at the Extended Follow-up visit
Appendix 5 Table 7 Clinical Laboratory tests	Deletion of the fasting glucose test	Only normal non-fasting glucose testing will be performed

Table of Contents

1 Protocol Summary

1.1 Synopsis

Protocol Title:

Open-label, Phase III efficacy and safety study of L-praziquantel orodispersible tablets (L-PZQ ODT) in Schistosoma-infected children 3 months to 6 years of age, including a 2:1 randomized, controlled cohort of Schistosoma mansoni-infected children 4 to 6 years of age treated with L-PZQ ODT or commercial PZQ (Biltricide®)

Short Title:

Phase III pediatric study with L-PZQ ODTs

Rationale:

This is a Phase III safety/efficacy study in Schistosoma-infected African children 3 months to 6 years of age and it is part of the PZQ ODT clinical development program, which aims to register a single dose of the new ODTs in the targeted pediatric age group (3 months to 6 years of age).

The rationale for this study is based on data gathered from previously conducted Phase I and Phase II clinical studies with the new PZQ ODTs.

Objectives and Endpoints:

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe
Primary		
To assess the efficacy of a single dose (50 mg/kg) of L-PZQ ODT as assessed by cure rate 17 to 21 days after treatment, in children 4 to 6 years of age infected with S. mansoni (Treatment group 1a). The efficacy of a single dose (40 mg/kg) of commercial PZQ tablets (Biltricide) in the same patient population (Treatment group 1b) will be considered as an internal control.	Clinical cure is defined as no parasite eggs in the stool 17 to 21 days after treatment. Egg counts will be determined by the Kato-Katz method: One stool sample will be collected during the pre screening period (Day -28 to Day -1) and the second one within a maximum of 5 days thereafter as baseline. Two additional stool samples will be collected between Day 17 to 21 after dosing to determine efficacy: the first one will be collected within the 17 to 21-day window and the second one within a maximum of 5 days following	End-of-Study visit (17 to 21 days after treatment)

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe
	collection of the 1st sample. Three Kato-Katz thick smears (41.7 mg) will be prepared from each stool sample.	
Secondary		
To assess the safety of a single dose (50 mg/kg) of L-PZQ ODT in children 4 to 6 years of age infected with S. mansoni (Treatment group 1a)	Safety and tolerability assessments: - Occurrence, nature, severity and outcome of adverse events (AEs), - Occurrence of treatment-related AEs - Changes in laboratory safety parameters (hematology, biochemistry, urinalysis) and vital signs (body temperature, blood pressure and pulse rate)	First treatment to planned End-of-Study visit
To assess the efficacy of a single dose (50 mg/kg) of L-PZQ ODT as assessed by cure rate 17 to 21 days after treatment, in children 2 to 3 years of age and in infants/toddlers 3 to < 24 months of age infected with S. mansoni (Cohorts 2 and 3, respectively)	Same as Cohort 1.	End-of-Study visit
To assess the safety of a single dose (50 mg/kg) of L-PZQ ODT in children 2 to 3 years of age and in infants/toddlers 3 months to < 24 months of age infected with S. mansoni (Cohort 2 and 3, respectively)	Same as Cohort 1.	First treatment to planned End-of-Study visit
To assess the efficacy of a single dose (50 mg/kg, 60 mg/kg based on IDMC) of L-PZQ ODT as assessed by cure rates 17 to 21 days and 35 to 40 days after treatment, in children 3 months to 6 years of age infected with S. haematobium	Clinical cure is defined as no parasite eggs in the urine samples at follow-up. Egg counts will be determined by urine examination using the urine filtration technique: The first sample	End-of-Study visit and Extended Follow-up visit

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe
(Cohort 4)	will be collected during the pre screening period (Day -28 to Day -1) and the second and the third one within a maximum of 5 days thereafter as baseline. At the End-of-Study visit (between Days 17 and 21) Cohort 4 participants will be asked to provide three urine samples (about 10 mL each): the first one will be collected within the 17 to 21-day window and the other two within a maximum of 5 days following collection of the 1st sample, for analysis by the filtration method. Similarly, at the Extended Follow-up visit, Cohort 4 participants will be asked to provide three additional urine samples (about 10 mL each) on different days between Day 35 and Day 40, for efficacy assessment by the filtration method. The urine samples will be filtered through a filter mesh. This mesh is then examined under the microscope for S. haematobium egg count.	
To assess the safety of a single dose (50 mg/kg, 60 mg/kg based on IDMC) of L-PZQ ODT in children 3 months to 6 years of age infected with S. haematobium (Cohort 4)	Same as Cohort 1	First treatment to planned End-of-Study visit
To assess the efficacy of a single dose (50 mg/kg) of the L-PZQ ODT as assessed by egg reduction rate (ERR) 17 to 21 days after treatment, in children 4 to 6 years of age infected with S. mansoni (Treatment group 1a). The efficacy (ERR) of a single dose (40 mg/kg) of commercial PZQ tablets (Biltricide) in the same patient population (Treatment group 1b)	ERR from pretreatment to 17 to 21 days after treatment, using parasite egg counts as determined by the Kato-Katz method for Cohort 1.	Pre screening visit to End-of-Study visit

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe
will be considered as an internal control.		
To assess the efficacy of a single dose (50 mg/kg) of L-PZQ ODT as determined by ERR in children 2 to 3 years of age and in infants and toddlers 3 months to < 24 months of age infected with S. mansoni (Cohorts 2 and 3, respectively). And in children 3 months to 6 years of age infected with S. haematobium (Cohort 4; 50 mg/kg, 60 mg/kg based on IDMC)	ERR from pre-treatment to 17 to 21 days after treatment, using parasite egg counts as determined by the Kato-Katz method for Cohorts 2 and 3 and the urine filtration method for Cohort 4. Additionally, ERR from pretreatment to 35 to 40 days after treatment, using parasite egg counts as determined by the urine filtration method for Cohort 4 participants.	Pre screening visit to End-of-Study visit and Extended Follow-up visit
To assess the cure rate as demonstrated with use of the commercially available point-of-care circulating cathodic antigen (POC-CCA®) test (Cohorts 1, 2, and 3).	One urine sample will be collected 17 to 21 days after treatment. Cure is defined as absence of test line in the POC-CCA® test cassette (i.e., no Schistosoma antigens detected).	End-of-Study visit
To assess acceptability in terms of ease of administration of the selected ODT (Treatment group 1a, Cohorts 2, 3, and 4) and commercial PZQ tablet (Treatment group 1b)	Reaction to Study Intervention administration (e.g., spitting, crying) to describe tolerability as assessed by nurse/site staff for all children enrolled in the study. Palatability assessment using a human gustatory sensation test (100-mm visual analogue scale [VAS]) scoring modified by the incorporation of a 3-point facial hedonic scale for all children 5 and 6 years of age enrolled in the study.	At Study Intervention administration
To assess the concentration-time profile of the L-PZQ ODT formulation and Biltricide formulation in a subset of children	Concentrations of R-(-)-PZQ and rac-PZQ, and if appropriate, pharmacokinetics (PK) parameters (e.g., C_{max}, t_{max}, AUC_{0-t})	Pre dose to 12 hours afterwards

Overall Design:

This is a multicenter open-label Phase III study in which participants assigned to 1 of 4 cohorts based on age (infants and children 3 months to 6 years of age) and Schistosoma species of infection will receive at Day 1 a single treatment dose of L-PZQ ODT 50 mg/kg (see Section 1.3 Schedule of Activities). The study includes 2:1 randomization of children 4 to 6 years of age infected with S. mansoni (Cohort 1, n= 150) to the PZQ ODT treatment (Treatment group 1a) or the control treatment (40 mg/kg racemic PZQ [rac-PZQ] crushed tablets, Treatment group 1b). S. mansoni-infected children 2 to 3 years of age (Cohort 2, n= 30), S. mansoni-infected children 3 to < 24 months of age (Cohort 3, n= 25 to 65) and S. haematobium-infected children 3 months to 6 years of age (Cohort 4, n= 60 to 90) will be treated with a single dose of 50 mg/kg of L-PZQ ODT. Upon recommendation of the Independent Data Monitoring Committee (IDMC), the dose administered to participants in Cohort 4 may be increased to 60 mg/kg[a]. No randomization is foreseen in Cohorts 2, 3, and 4.

Number of Participants:

The primary endpoint will be the cure rate computed by treatment group on the modified intention-to-treat (mITT) population of 4 to 6 years of age children infected with S. mansoni (Cohort 1). A total of 150 participants will be randomized 2:1 into the L-PZQ ODT treatment group or the commercial rac-PZQ (Biltricide) treatment group and analyzed similarly; however, the efficacy of the two treatments will not be compared statistically. The commercial rac-PZQ treatment arm as an active control arm will be considered an internal benchmark. The sample size of n= 150 for Cohort 1 was chosen based on the precision of the estimate of the true cure rate.

For a fixed sample size, the precision of the estimate of the true cure rate is dependent on the observed cure rate. In Part 1 of the Phase II study, MS200661-0005, the observed cure rate in the mITT population for L-PZQ ODT 45 mg/kg among children 4 to 6 years of age was 83.7% (36/43 cured; 95% confidence interval [CI]: 69.3-93.2). With 95 participants in the Phase III mITT Analysis Set receiving L-PZQ ODT in Treatment group 1a, the lower bound of a two-sided 95% CI for a single proportion using the Clopper-Pearson exact method will extend 10.0% from the observed proportion for an expected cure rate of 73.7%.

Assuming 5% of participants will need anti-malarial treatments after PZQ treatment and a 20% non-evaluable rate, a total of 150 participants will be randomized in Cohort 1, according to a 2:1 ratio, to achieve 95 mITT participants and 80 per-protocol (PP) participants exposed to the L-PZQ ODT and 47 mITT and 40 PP participants exposed to commercial rac-PZQ tablets (Biltricide). The mITT population will be used to analyze the primary endpoint.

In Cohort 2, a total of 30 participants 2 to 3 years of age infected with S. mansoni will be enrolled to assess consistency of the treatment effect with that in the older age group. The size of Cohort 2 is 30% of that of Treatment group 1a, to be roughly consistent with the distribution of

[a] An Independent Data Monitoring Committee (IDMC) meeting was held on the 09 March 2020 and a decision was made to increase the dose in Cohort 4 to 60 mg/kg.

children 2 to 3 years of age (27%) and 4 to 6 years of age (73%) enrolled in the Phase II study, in which no differences in cure rate by age were observed.

In Cohort 3 overall, a total of 65 participants 3 to 24 months of age infected with S. mansoni will be enrolled in the Phase II and Phase III studies. The sample size in either study alone is too small to have adequate precision on the cure rate, thus the results in this Phase III study (Cohort 3) will be pooled with Cohorts 8 and 9 of the ongoing Phase II study (MS200661-0005). Planned enrollment in Study MS200661-0005 is up to 30 participants 13 to 24 months of age and up to 10 participants 3 to 12 months of age. In Cohort 3 of this Phase III study, at least 25 participants 3 to 24 months of age infected with S. mansoni (i.e., ~20% of the total number of participants 2 to 6 years of age receiving L-PZQ ODT) will be enrolled. If the enrollment of this age group from Phase II is lower than planned, then more than 25 participants will be enrolled in Phase III Cohort 3 to achieve a total of 65 participants in this age group. This pooled sample will allow a general comparison to assess whether the treatment effect is similar across age groups.

A maximum of 90 children will be enrolled in Cohort 4. A total of 60 children in Cohort 4, 3 months to 6 years of age infected with S. haematobium, will be treated with L-PZQ ODT at the final dose, either 50 mg/kg or 60 mg/kg. Sample size is based on the number of participants needed to provide a meaningful estimate of cure rate in the S. haematobium-infected participants.

In summary, a total of 265 to 335 children will be enrolled and allocated to 4 cohorts as follows:

- Cohort 1: 150 children (4 to 6 years of age) infected with S. mansoni, randomized 2:1 into Treatment 1a and Treatment 1b.
- Cohort 2: 30 participants, 2 to 3 years of age, infected with S. mansoni.
- Cohort 3: 25 to 65 participants (the target is to have a total of 65 children in the pooled analysis with Phase II, MS200661-0005, Cohorts 8 and 9), 3 months to 24 months of age, infected with S. mansoni.
- Cohort 4: 60 to 90 children, 3 months to 6 years of age, infected with S. haematobium. A total of 60 children in Cohort 4, 3 months to 6 years of age infected with S. haematobium, will be treated with L-PZQ ODT at the final dose either 50 mg/kg or 60 mg/kg. The final dose will depend on the efficacy results of the initially selected 50 mg/kg dose, based on an interim assessment of 30 participants.

Study Intervention Groups and Duration:

A maximum 28-day pre screening and screening period, followed by a single treatment on Day 1 and 17 to 21 days of follow-up are foreseen for each participant, with a total study duration of up to 7 weeks for a given participant. In Cohort 4 subjects treated with 60 mg/kg, an additional urine collection is planned at Days 35 to 40, leading to a study duration of 9 weeks. Duration of the Study Intervention period is foreseen to be up to 6 months.

Involvement of Special Committee(s):

An Independent Data Monitoring Committee (IDMC) will be in charge of reviewing the safety data of the Phase III. The IDMC will also evaluate the efficacy data of Cohort 4 (S. haematobium-infected children 3 months to 6 years of age) after 30 children have been

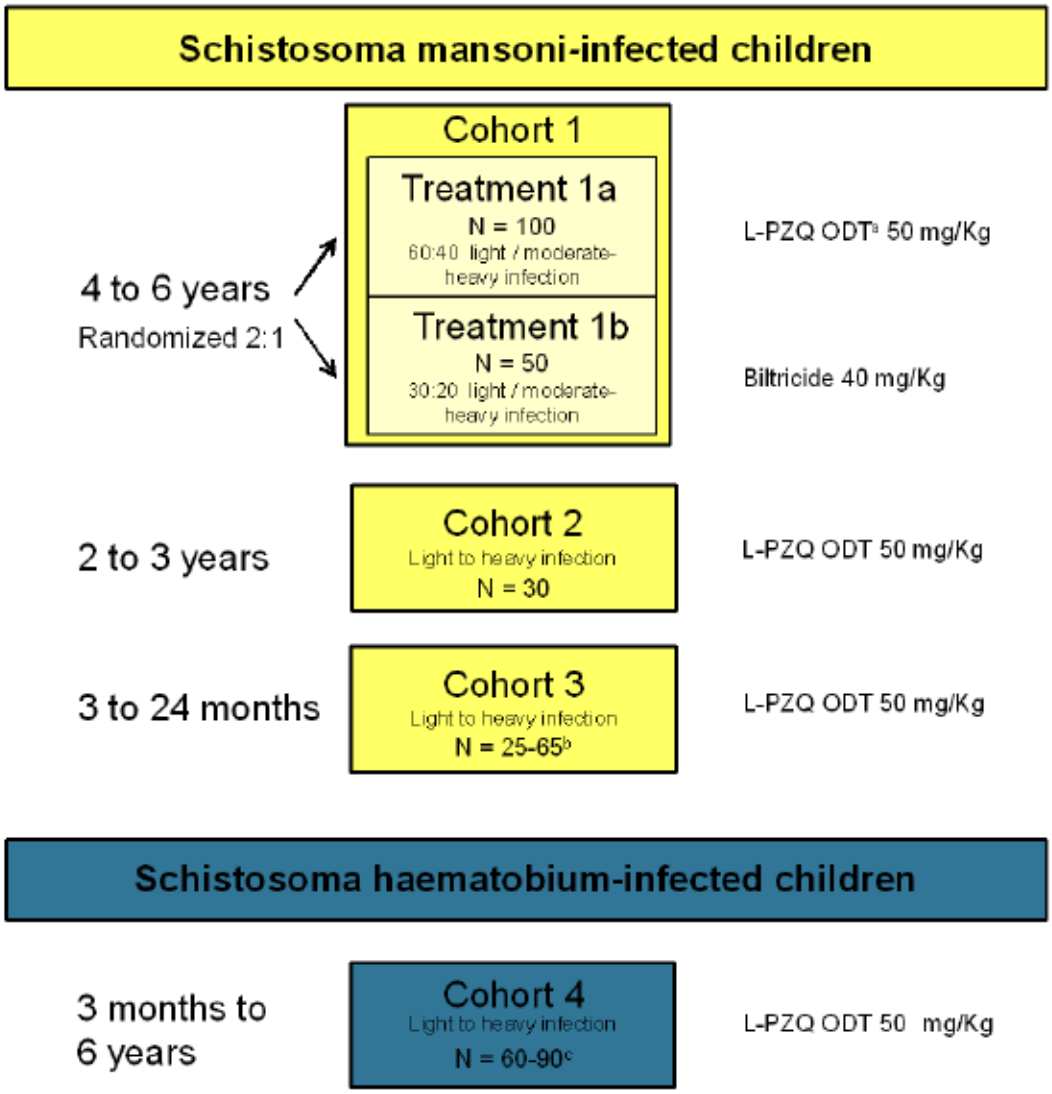
treated with L-PZQ ODT 50 mg/kg and will decide if a dose increase to 60 mg/kg is needed (see IDMC charter for additional details). The IDMC will consist of a Pediatrician specializing in Schistosomiasis and deemed a global expert, a medical doctor in an endemic country and a biostatistician.

The Safety Monitoring Committee (SMC) has reviewed the safety and efficacy data available on the first 10 participants from Cohort 8 enrolled in Part 2 of Phase II study, MS200661-0005 and deemed them satisfactory. As this was a prerequisite for the enrollment of Cohort 3 in the Phase III study, MS20061-0003, the enrollment of this cohort will take place as planned.

1.2 Schema

The proposed Phase III study consists of 4 cohorts, to be enrolled in parallel, as shown in Figure 1.

Figure 1 Design Diagram



[a] Levo-Praziquantel Orodispersible Tablet
[b] 65 participants are requested in pooled analysis with Phase 2, MS200661-0005, Cohorts 8 and 9. If the target number is not reached in those two cohorts, additional patients will be enrolled in Cohort 3
[c] After 30 patients in Cohort 4 are treated, the efficacy data will be evaluated by the IDMC to decide whether an increase of the dose to 60 mg/kg is needed, in which case 30 additional patients will be added to this cohort and treated with the 60 mg/kg dose

1.3 Schedule of Activities

Assessments & Procedures	Pre Screening[1]	Screening	Treatment									End of Confinement visit	Follow-up	End-of Study visit	Extended Follow-up[9]
Day/Time of the Assessment	Day -28 to Day -1	Day -7 to Day 1	Day 1									Hours 12[2] to 24	Day 3 to Day 4[3]	Day 17 to Day 21	Day 35 to Day 40
Time of the Assessment		Pre dose	H0	H0.5	H1	H2	H3	H4	H6	H8	H12				
Pre screening Informed Consent Form (ICF) signature	X														
ICF signature[20]		X													
Urine POC-CCA® test[4]	X[5]													X[5]	
Stool examination by Kato-Katz	X[6]													X[7]	
Urine filtration	X[8]													X[9]	X
Malaria rapid diagnostic test	(X)[10]	X													
Safety laboratory tests (haematology, biochemistry, urinalysis)		X									X				
Demographics	X														
Demographics, medical history and history of medication		X													
Vital signs (BP, Pulse Rate, Temperature)		X[11]								X		X		X	
Physical examination (incl height & weight)		X										X[12]		X	
Inclusion/exclusion criteria		X													
Cohort allocation		X													
Confinement[13]		X	X	X	X	X	X	X	X	X	X	X			
Food administration		X[14]						X[15]		X[15]					
Administration of Study Intervention			X												
Reaction to Study Intervention			X	X	X	X	X	X	X	X	X				
Palatability[16]			X												

Pharmacokinetics (PK) sampling (subset of participants only)[17]		X[18]		X[19]	X[19]	X[19]	X[19]	X[19]	X[19]	X[19]	X[19]				
AE and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Pre screening will be conducted in the villages. For Cohorts 1 through 3, only children who are positive for S. mansoni and negative for S. haematobium will be transferred to the hospital for further screening. For Cohort 4, only children who are positive for S. haematobium and negative for S. mansoni will be transferred to the hospital for further screening.
[2] If the participant, for logistical or social reasons, has to remain in hospital an additional night, the confinement may end up to 24 hours after dosing. At end of confinement, vital signs will be recorded and a physical examination performed.
[3] Follow-up of Adverse Event (AE), if required.
[4] POC-CCA cassettes will be classified as either positive or negative, according to the manufacturer's instructions, with further stratification depending on the strength of the color reaction. Thus, positive cassettes will be classified as + 1 (when result line is easy to see but still weak), + 2 (when result line is dark, but lighter than the control line) or + 3 (when result line is as dark as or darker than the control line).
[5] For Cohorts 1 through 3 only
[6] Cohort 1 to 3: two stool samples collected within 5 days during the pre screening period. Three Kato-Katz smears will be prepared from each of the stool samples to determine S. mansoni egg counts. For Cohort 4: a stool sample will be collected during the pre screening period. Two Kato Katz smears will be prepared from the sample to evaluate the presence of S. mansoni eggs.
[7] For Cohorts 1 through 3 only. A stool sample will be collected between Day 17 to 21 days after dosing and another one within 5 days thereafter.
[8] For Cohorts 1-3, one urine sample (about 10 mL) will be filtered through a filter mesh and the mesh examined under the microscope to exclude the presence of S. haematobium eggs. For Cohort 4: three urine samples (about 10 mL each), collected within 5 days, will be filtered through a filter mesh and the mesh will be subsequently examined under the microscope for S. haematobium egg count.
[9] Cohort 4 only in case treated with 60 mg/kg L-PZQ ODT.
[10] Malaria Rapid Diagnostic Test can be done at discretion of investigator during pre screening.
[11] Before PK samples are taken.
[12] Height only at screening
[13] Confinement from the morning of the dosing until at least 12 hours after the Study Intervention administration.
[14] Within one hour before dosing
[15] Participants should fast for 4 hours after dosing if they are in the PK subset. For all other study participants, food can be given at the discretion of the Investigator
[16] Palatability assessment will be done using a human gustatory sensation test (100-mm VAS) scoring modified by the incorporation of a 3-point facial hedonic scale (for children 5 and 6 years of age only).
[17] For children with body weight of less than 10 kg, please see Section 8.5 for details.
[18] Just before dosing
[19] The allowed deviation from the pre-specified assessment will be ± 10% (in minutes) of the scheduled time point. In case several assessments are planned at the same time point, the PK samples will be taken at the pre-defined time point.
[20] If screening procedures are repeated (e.g due to temporal exclusion of participant for more than 7 days) the Informed consent form does not need to be resigned

2 Introduction

Praziquantel (PZQ), the current standard treatment against schistosomiasis (or bilharzia), is a racemic mixture composed of the R-(-)-PZQ and S-(+)-PZQ enantiomers in a 1:1 ratio. The cidal activity resides in the R-(-)-PZQ enantiomer (as shown in vitro and in animal experiments [6]) whereas the S-(+)-PZQ enantiomer was suggested to be largely responsible for the bitterness of the commercial formulation.

The new L-PZQ formulation has now been manufactured as a solid oral dosage form which can be administered as an orodispersible tablet or dispersible tablet (for simplicity, the formulation will be referred to as "ODT" throughout this document) and has shown better palatability as compared with the rac-PZQ 600 mg commercial product (study EMR200661-002). In this study, Schistosoma-infected African children 3 months to 6 years of age will receive a single dose of 50 mg/kg (as determined by the data from Part 1 of the Phase II study, MS200661-0005). For Cohort 4 (S. haematobium-infected children) only, the IDMC may decide to increase the proposed dosage to 60 mg/kg after review of efficacy and safety data for the first 30 enrolled participants.

Complete information on the chemistry, pharmacology, efficacy, and safety of the L-PZQ ODT formulation is in the Investigator's Brochure (IB) version 4.**Study Rationale**

This is a Phase III safety/efficacy study in Schistosoma-infected African children 3 months to 6 years of age and it is part of the PZQ ODT clinical development program, which aims to register a single dose of the new ODTs in the targeted pediatric age group (3 months to 6 years of age).

The program has been designed in line with existing International Council for Harmonisation/European Union/United States Food and Drug Administration (ICH/EU/FDA) pediatric development guidance documents and recommendations, including the ICH E11 Guideline, the European Medicines Agency (EMA) Reflection Paper on extrapolation of efficacy and safety in pediatric medicine development, the FDA guidance of 2014 for pediatric development, as well as other applicable EU and FDA guidance for the development of chiral drugs, including the EU Guideline on the Investigation of Chiral Active Substances (April 1994).

The rationale for this study is based on data gathered from previously conducted Phase I and Phase II clinical studies with the new PZQ ODTs (summarized in Section 4.2).

2.2 Background

Schistosomiasis, also called bilharzia, is one of the most important of the neglected tropical diseases caused by flatworms and remains one of the most prevalent parasitic diseases in developing countries. In terms of impact, this disease is second only to malaria as the most devastating parasitic disease, with significant economic and public health consequences. Schistosomiasis is a severe chronic inflammatory disease that is endemic in about 78 developing countries. More than 258 million people are infected, with more than 90% of them living in Africa, particularly in rural agricultural and peri-urban areas. More than 700 million people are at

risk. In many areas, schistosomiasis infects a large proportion of children under the age of 14 years, including an estimated 28 million preschool-age children (PSAC). In these very young children, local prevalence of infection may exceed 60% (Report of a meeting to review the results of studies on the treatment of schistosomiasis in preschool-age children, WHO, Geneva, Switzerland, 13–14 September 2010).

There are two major forms of schistosomiasis—intestinal and urogenital—caused by five main species of blood fluke. The most prevalent species in Sub-Saharan Africa (SSA) are S. mansoni (intestinal schistosomiasis) and S. haematobium (urogenital schistosomiasis). Urogenital schistosomiasis is also considered to be a risk factor for human immunodeficiency virus (HIV) infection, especially in women.

The World Health Organization (WHO)-recommended strategy to control morbidity caused by schistosomiasis is based on preventive chemotherapy interventions targeting the majority of the at-risk population. The current gold standard treatment employs an annual, single oral dose (40 mg/kg) of PZQ tablets. PZQ was jointly developed by Bayer AG and Merck KGaA in the 1970's and commercialized in 1980 as Biltricide (Bayer AG), Cesol®/Cysticide®/Cisticid® (Merck KGaA) for human use, and subsequently as other generic products. PZQ has been used over the subsequent years to control schistosomiasis in many countries. In 2012 more than 35 million people, 83% of them in SSA, were treated for schistosomiasis. Over all these years of treatment, PZQ tablets have shown a good safety and tolerability profile in previous studies, in the recently published meta-analysis in children[1] and according to the most recent Periodic Benefit-Risk Evaluation Report (PBRER).

At the World Health Assembly in 2001, Resolution A 54.19 was put forward, "which urged endemic countries to start seriously tackling worms, specifically schistosomiasis and soil- transmitted helminths (STH)", with a global target to treat at least 75% of all school-age children who are at risk of morbidity from schistosomiasis and STH by the year 2010. In 2013, the World Health Assembly passed Resolution 66.20, in which the Member States essentially confirmed their commitment to fulfill the WHO 2020 Roadmap for the elimination of neglected tropical diseases (including schistosomiasis) or reductions in their impact to levels at which they are no longer considered public-health problems. PSAC, who are a high-risk group for schistosome infections, are currently not included in the WHO schistosomiasis control programs. In 2012, the WHO formally recognised that infants and PSAC are at significant risk of schistosomiasis and qualify for treatment with PZQ.

In order to tackle this important public health problem, a pediatric schistosomiasis consortium was formed in July 2012 under the leadership of Merck KGaA, with the goal of developing and registering a suitable pediatric formulation of PZQ for use in PSAC. The consortium currently consists of 8 partners: Merck KGaA (Germany), Lygature (Netherlands), Astellas Pharma Inc. (Japan), Swiss Tropical and Public Health Institute (Switzerland), Farmanguinhos Fiocruz Foundation (Brazil), the Schistosomiasis Control Initiative (UK), Université Félix Houphouët-Boigny (Ivory Coast) and the Kenya Medical Research Institute (Kenya). SimCyp (UK) exited the Consortium in August 2017, after completion of their modeling and simulation activities.

2.3 Benefit/Risk Assessment

Over the past 40 years, rac-PZQ tablets have shown a good safety and tolerability profile in previous trials, in the recently published meta-analysis in children (Zwang J, et al. 2014)[1] and according to the recently prepared Periodic Benefit-Risk Evaluation Report (PBRER). In the meta-analysis, 273 studies were identified; thereof, 55 studies were deemed eligible (19,499 participants treated with PZQ, control treatment or placebo). Most studies involved school- age children (64%) infected with S. mansoni (58%) and treated with a 40 mg/kg dose (56%); 68% of participants were in Africa. Tolerability was assessed in 40 studies (12,435 participants) as Adverse Event (AE) incidence. On average, 56.9% (95% CI: 47.4, 67.9) of the participants receiving PZQ 40 mg/kg experienced an AE. The incidence of AEs ranged from 2.3% for urticaria to 31.1% for abdominal pain.

The data from the PZQ ODT Phase I study (EMR200661-001) was consistent with the already well-established safety profile for the rac-PZQ tablets and also demonstrated good safety and tolerability for L-PZQ ODTs in adults. At similar exposure levels, fewer treatment-emergent adverse events (TEAEs) were observed with L-PZQ ODT than with rac-PZQ, although the number of enrolled subjects was small. The most common AEs after administration of PZQ are gastrointestinal effects: diarrhea, nausea, vomiting and abdominal pain, as well as transient neurological effects (headache and dizziness), although dizziness was not observed after L-PZQ ODT administration in the Phase I study. Regarding general disorders, the following AEs have been reported in post marketing settings: weakness, fatigue and increased body temperature. All of these symptoms were usually transient, and they resolved spontaneously. Adverse reactions, including hypersensitivity reactions, which may partly represent endogenous reactions to the killing of the parasites by PZQ, were not observed in the Phase I study with L-PZQ ODT in healthy volunteers. For patients suffering from schistosomiasis, this underlying parasitosis could also mask the AEs of PZQ treatment, e.g., Katayama syndrome, which is an early clinical manifestation of schistosomiasis occurring several weeks post infection with Schistosoma spp (trematode) worms. The disease onset appears to be related to migrating schistosomula and egg deposition, with individuals typically presenting with nocturnal fever, cough, myalgia, headache, and abdominal tenderness (Ross et al., 2007)[2]

An acceptable safety profile for the PZQ ODTs was also observed in Part 1 of the Phase II study (MS200661-0005) in children 2 to 6 years of age infected with S mansoni. The safety summary data from Part 1 of this study did not show any TEAEs leading to death and no withdrawals due to AEs. Among a total of 420 participants randomized, 64 (15.2%) participants reported 68 drug-related TEAEs. The drug-related TEAEs were mostly mild (42) and moderate (25) in intensity, with only one severe TEAE in Cohort 3 (rac-PZQ ODT 40 mg/kg), which could be explained alternatively (underlying malaria, and hepatic fibrosis due to chronic hepatosplenic schistosomiasis). Two unlisted TEAEs assessed by the Investigator as drug-related have never been reported before with PZQ. These TEAEs were reported in Cohort 4 (rac-PZQ ODT 60 mg/kg): gastroenteritis (in 3 participants) and thrombocytopenia (in 1 participant). These TEAEs could not be explained by the mechanism of action of PZQ.

Only TEAEs reported in the System Organ Class (SOC) Gastrointestinal disorders occurred in > 10% of participants: abdominal pain (25), vomiting (11), diarrhoea (10)/diarrhoea

haemorrhagic (1), and nausea (2). Cohort 6 (L-PZQ ODT 45 mg/kg) had the lowest number of participants with study intervention-related TEAEs (2) and Cohort 4 (rac-PZQ ODT 60 mg/kg) had the highest number (16), with the other cohorts in between (Cohort 3, 40 mg/kg rac-PZQ ODT – 6 TEAEs; Cohort 5, 30 mg/kg L-PZQ ODT – 8 TEAEs; Cohort 1, Biltricide 3x20 mg/kg – 9 TEAEs; Cohort 2, Biltricide 40 mg/kg – 11 TEAEs, and Cohort 7, 60 mg/kg L-PZQ ODT – 12 TEAEs). Most TEAEs were transient and resolved spontaneously, generally not requiring any special treatment.

Post treatment complaints, whether reported by patients or health care providers, can be caused directly by PZQ (I, direct relationship), can be regarded as an endogenous reaction to the killing of the parasites by PZQ (II, indirect relationship) or else, can represent signs and symptoms of the parasitic infection (III, no relationship). It is often difficult to reliably differentiate between possibilities I, II and III.

PZQ is contraindicated in individuals with a history of proven hypersensitivity to PZQ or any of the excipients; in intraocular cysticercosis; and in combination with rifampicin. Caution is warranted in decompensated hepatic insufficiency or in patients with hepatosplenic schistosomiasis. Those with cardiac arrhythmias should be monitored during therapy. The same applies to patients with heart failure requiring digitalis therapy, since a digitalis-antagonistic effect has been demonstrated in animal studies.

The cumulative post authorization exposure to PZQ since January 2009 to May 2017 is estimated to be about 972,535 patients (Development Safety Update Report, reporting period 26 May 2016 to 25 May 2017).

More detailed information about the known and expected benefits and risks and reasonably expected AEs following administration of the L-PZQ ODT may be found in Section 4.2 (Scientific Rationale for Study Design) and the IB. Based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

3 Objectives and Endpoints

Table 1 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe
Primary		
To assess the efficacy of a single dose (50 mg/kg) of L-PZQ ODT as assessed by cure rate 17 to 21 days after treatment, in children 4 to 6 years of age infected with S. mansoni (Treatment group 1a). The efficacy of a single dose (40 mg/kg) of commercial PZQ tablets (Biltricide) in the same patient population (Treatment group 1b) will be considered as an internal control.	Clinical cure is defined as no parasite eggs in the stool 17 to 21 days after treatment. Egg counts will be determined by the Kato-Katz method: One stool sample will be collected during the pre screening period (Day -28 to Day -1) and the second one within a maximum of 5 days thereafter as baseline. Two additional stool samples will be collected between Day 17 to 21 after dosing to determine efficacy: the first one will be collected within the 17 to 21 day window and the second one within a maximum of 5 days following collection of the 1st sample. Three Kato-Katz thick smears (41.7 mg) will be prepared from each stool sample.	End-of-Study visit (17 to 21 days after treatment)
Secondary		
To assess the safety of a single dose (50 mg/kg) of L-PZQ ODT in children 4 to 6 years of age infected with S. mansoni (Treatment group 1a)	Safety and tolerability assessments: - Occurrence, nature, severity and outcome of adverse events (AEs), - Occurrence of treatment-related AEs - Changes in laboratory safety parameters (hematology, biochemistry, urinalysis) and vital signs (body temperature, blood pressure and pulse rate)	First treatment to End-of-Study visit

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe
To assess the efficacy of a single dose (50 mg/kg) of L-PZQ ODT as assessed by cure rate 17 to 21 days after treatment, in children 2 to 3 years of age and in infants/toddlers 3 to < 24 months of age infected with S. mansoni (Cohorts 2 and 3, respectively)	Same as Cohort 1.	End-of-Study visit
To assess the safety of a single dose (50 mg/kg) of L-PZQ ODT in children 2 to 3 years of age and in infants/toddlers 3 months to < 24 months of age infected with S. mansoni (Cohort 2 and 3, respectively)	Same as Cohort 1.	First treatment to End-of-Study visit
To assess the efficacy of a single dose (50 mg/kg, 60 mg/kg based on IDMC) of L-PZQ ODT as assessed by cure rate 17 to 21 days and 35 to 40 days after treatment, in children 3 months to 6 years of age infected with S. haematobium (Cohort 4)	Clinical cure is defined as no parasite eggs in the urine samples at follow-up. Egg counts will be determined by urine examination using the urine filtration technique: The first sample will be collected during the pre screening period (Day -28 to Day -1) and the second and the third one within a maximum of 5 days thereafter as baseline. At the End-of-Study visit (between Days 17 and 21) Cohort 4 participants will be asked to provide three urine samples (about 10 mL each): the first one will be collected within the 17 to 21-day window and the other two within a maximum of 5 days following collection of the 1st sample, for analysis by the filtration method. Similarly, at the Extended Follow-up visit, Cohort 4 participants will be asked to provide three additional urine samples (about 10 mL each) on	End-of-Study visit and Extended Follow-up visit

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe
	different days between Day 35 and Day 40, for efficacy assessment by the filtration method. The urine samples will be filtered through a filter mesh. This mesh is then examined under the microscope for S. haematobium egg count.	
To assess the safety of a single dose (50 mg/kg, 60 mg/kg based on IDMC) of L-PZQ ODT in children 3 months to 6 years of age infected with S. haematobium (Cohort 4)	Same as Cohort 1.	First treatment to planned End-of-Study visit
To assess the efficacy of a single dose (50 mg/kg) of the L-PZQ ODT as assessed by egg reduction rate (ERR) 17 to 21 days after treatment, in children 4 to 6 years of age infected with S. mansoni (Treatment group 1a). The efficacy (ERR) of a single dose (40 mg/kg) of commercial PZQ tablets (Biltricide) in the same patient population (Treatment group 1b) will be considered as an internal control.	ERR from pretreatment to 17 to 21 days after treatment, using parasite egg counts as determined by the Kato-Katz method for Cohort 1.	Pre screening visit to End-of-Study visit
To assess the efficacy of a single dose (50 mg/kg) of L-PZQ ODT as determined by ERR in children 2 to 3 years of age and in infants and toddlers 3 months to < 24 months of age infected with S. mansoni (Cohorts 2 and 3, respectively). And in children 3 months to 6 years of age infected with S. haematobium (Cohort 4; 50 mg/kg, 60 mg/kg based on IDMC).	ERR from pretreatment to 17 to 21 days after treatment, using parasite egg counts as determined by the Kato-Katz method for Cohorts 2 and 3 and the urine filtration method for Cohort 4. Additionally, ERR from pretreatment to 35 to 40 days after treatment, using parasite egg counts as determined by the urine filtration method for Cohort 4 participants.	Pre screening visit to End-of-Study visit and Extended Follow-up visit
To assess the cure rate as demonstrated with use of the commercially available	One urine sample will be collected 17 to 21 days after treatment. Cure is defined as absence of test line in the	End-of-Study visit

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe
point-of-care circulating cathodic antigen (POC-CCA®) test (Cohorts 1, 2, and 3).	POC-CCA® test cassette (i.e., no Schistosoma antigens detected).	
To assess acceptability in terms of ease of administration of the selected ODT (Treatment group 1a, Cohorts 2, 3, and 4) and commercial PZQ tablet (Treatment group 1b)	Reaction to Study Intervention administration (e.g., spitting, crying) to describe tolerability as assessed by nurse/site staff for all children enrolled in the study. Palatability assessment using a human gustatory sensation test (100-mm visual analogue scale [VAS]) scoring modified by the incorporation of a 3-point facial hedonic scale for all children 5 and 6 years of age enrolled in the study.	At Study Intervention administration
To assess the concentration-time profile of the L-PZQ ODT formulation and Biltricide formulation in a subset of children	Concentrations of R-(-)-PZQ and rac-PZQ and, if appropriate, pharmacokinetics (PK) parameters (e.g., C_{max}, t_{max}, AUC_{0-t})	Pre-dose to 12 hours afterwards

4 Study Design

4.1 Overall Design

This is a multicenter open-label Phase III study in which participants assigned to 1 of 4 cohorts based on age (infants and children 3 months to 6 years of age) and Schistosoma species of infection will receive at Day 1 a single treatment dose of L-PZQ ODT 50 mg/kg (see Section 1.3 Schedule of Activities). The study includes 2:1 randomization of children 4 to 6 years of age infected with S. mansoni to the PZQ ODT treatment (Treatment group 1a) (n= 100) or the control treatment (40 mg/kg racemic PZQ crushed tablets, Treatment group 1b) (n= 50). S. mansoni-infected children 2 to 3 years of age (n= 30) (Cohort 2), S. mansoni-infected children 3 to < 24 months of age (n= 25 to 65) (Cohort 3) and S. haematobium-infected children 3 months to 6 years of age (n= 60) (Cohort 4) will be treated with a single dose of 50 mg/kg of L-PZQ ODT. Upon recommendation of the IDMC, the dose administered to participants in Cohort 4 may be increased to 60 mg/kg.[3] No randomization is foreseen in Cohorts 2, 3, and 4.

A maximum 28-day pre screening and screening period, followed by a single treatment on Day 1 and 17 to 21 days of follow-up or 35 to 40 days (Cohort 4) (see Section 1.3 Schedule of Activities) are foreseen for each participant, with a total study duration of up to 7 or 10 weeks for a given participant. Duration of the Study Intervention period is foreseen to be up to 6 months.

The participants in Cohort 1 will be stratified according to their infection intensity, with target enrollment of 40% moderate/heavy infections and 60% of light infections. No stratification will be implemented for Cohorts 2, 3, and 4, or per sex or country. For Cohort 3, the target is to have a total of 65 participants in a pooled analysis with Phase II study (MS200661-0005) Cohorts 8 and 9. More than 25 participants may be enrolled in Cohort 3 if < 40 participants are enrolled in the Phase II study in this age group. After the treatment of the first 30 participants in Cohort 4, the efficacy and safety data will be evaluated by the IDMC to decide whether an increase of the dose to 60 mg/kg is needed; in such a case, 30 additional participants will be enrolled, i.e. total sample size of 90 for Cohort 4, n= 60 receiving the final dose.

4.2 Scientific Rationale for Study Design

This is an open-label study in which participants in 4 cohorts based on age and Schistosoma species of infection will receive a single treatment dose of the new L-PZQ ODT at Day 1. The study includes 2:1 randomization of children 4 to 6 years of age infected with S. mansoni to the PZQ ODT treatment (Treatment group 1a) or the control treatment (40 mg/kg racemic PZQ crushed tablets, Treatment group 1b). The control arm includes only children 4 to 6 years of age, since there is no approved agent to treat schistosomiasis for children < 4 years of age. The study is not powered for hypothesis testing, since the aim of Treatment group 1b is to act as an internal control, providing a benchmark for interpretation of the results observed in the L-PZQ ODT cohorts.

[3] An Independent Data Monitoring Committee (IDMC) meeting was held on the 09 March 2020 and a decision was made to increase the dose in Cohort 4 to 60 mg/kg.

An open-label design is considered appropriate, as the primary endpoint (cure rate) is assessed on the basis of objective assessment of egg counts. The study will be blinded for those laboratory personnel directly involved in the assessment of the Kato-Katz score.

The study design includes an open-label, randomized allocation of participants to L-PZQ ODT or Biltricide in Cohort 1, for whom marketed PZQ is approved by health authorities for the treatment of schistosomiasis in children ≥ 4 years of age. Schistosomiasis cure rates reported in the literature are heterogeneous across studies. Inclusion of the control group (Treatment group 1b) as a benchmark will help with interpretation of the Phase III study results, should they differ markedly from the Phase II study results.

Cohort allocation

- Cohort 1: S. mansoni-infected children 4 to 6 years of age (n= 150) will be randomized in a 2:1 ratio. Treatment group 1a, n= 100, will be treated with a single dose of 50 mg/kg of L-PZQ ODT (as the test treatment); Treatment group 1b, n= 50, will be treated with the reference PZQ commercial product (Biltricide 600 mg) crushed tablets at a single dose of 40 mg/kg (as the internal control treatment).
- Cohort 2: S. mansoni-infected children 2 to 3 years of age (n= 30) will be treated with a single dose of 50 mg/kg of L-PZQ ODT. The primary aim of the descriptive efficacy analysis in this cohort is to explore whether the treatment effect is consistent with the treatment effect in older children (not an independent proof of efficacy in this subgroup).
- Cohort 3: S. mansoni-infected infants and toddlers 3 to< 24 months of age (n= 25 to 65) will be treated with a single dose of 50 mg/kg of L-PZQ ODT. The primary aim of the descriptive efficacy analysis in this cohort is to explore whether the treatment effect is consistent with the treatment effect in older children (not an independent proof of efficacy in this subgroup).
- Cohort 4: S. haematobium-infected children 3 months to 6 years of age (n= 60) will be treated with a single dose of 50 mg/kg of L-PZQ ODT, to assess the safety and efficacy in this group (not an independent proof of efficacy in this subgroup). After 30 children are enrolled and treated in Cohort 4, the efficacy and safety data will be summarized and evaluated by the IDMC to decide whether there is a need to increase the dose to 60 mg/kg.[4] If a dose increase is needed, 30 additional patients will be added to this cohort (i.e., total sample size of 90 for Cohort 4, n= 60 receiving the final dose) and treated with the 60 mg/kg dose of L-PZQ ODT.

This study is part of the PZQ ODT clinical development program, which aims to register a single dose of L-PZQ ODTs in the targeted pediatric age group (3 months to 6 years of age). The rationale for the design of this study is also based on the information and data gathered from previously conducted Phase I and Phase II studies with the PZQ ODTs (summarized below) and takes into account feedback received from health authorities.

[4] An Independent Data Monitoring Committee (IDMC) meeting was held on the 09 March 2020 and a decision was made to increase the dose in Cohort 4 to 60 mg/kg.

4.2.1 Main Findings of the Phase I Studies with the New PZQ ODTs (MS200585-001 and MS200661-001)

The L-PZQ ODT formulation was assessed in a Phase I relative bioavailability (BA) study in adult healthy male volunteers (EMR200661-001), with the commercial rac-PZQ tablet (Cisticid® 500 mg) as a reference. The results showed a lower BA of the L-PZQ ODT (40% of the reference). The BA of the rac-PZQ ODT formulation was also assessed with the same reference in study EMR200585-001, showing comparable BA. The results pertaining to the L-PZQ ODT formulation are summarized in the IB v3.

4.2.2 Main Findings of the Phase I L-PZQ ODT Palatability Study (EMR200661-002)

The overall palatability of the L-PZQ ODT and the rac-PZQ ODT was tested in a taste study in Tanzanian children 6 to 11 years of age. Both formulations were found to have better palatability than the available PZQ product (Cesol 600 mg tablets) as assessed by means of human gustatory sensation tests (100-mm visual analogue scale (VAS) scoring, modified by the incorporation of a 5-point facial hedonic scale). No significant difference in VAS score was observed between the L-PZQ ODT and the rac-PZQ ODT.

Dispersion of the L-PZQ formulation in the mouth takes a bit more than 30 seconds. Thus, the proposed formulation may not meet a formal definition of "ODT" in all regions. Although a more precise naming might be "ODT-like", the formulation will be referred to as "ODT" in this document.

4.2.3 Main Findings of the Phase II Dose-finding Study in Ivory Coast (MS200661-0005)

Data from Part 1 of the Phase II study, MS200661-0005, recently completed in African children 2 to 6 years of age infected with S. mansoni (using different doses of rac-PZQ ODTs and L-PZQ ODTs as well as reference commercial rac-PZQ arms) showed that L-PZQ 60 mg/kg and L-PZQ 45 mg/kg had the highest efficacy, with cure rates of 90% (95% CI: 79%, 96%) and 86% (95% CI: 74%, 94%), respectively, in the mITT population.

Part II of this study is completed and has enrolled 20 S. mansoni-infected children 13 to 24 months of age in Cohort 8 and 4 S. mansoni-infected children 3 to 12 months of age in Cohort 9.

Detailed outcomes of the three studies are described in the IB.

4.2.4 Rationale for Study Population

Cohort 1

The primary aim of Cohort 1 is to assess the efficacy and safety of a single dose of the new L-PZQ ODT and a single dose of commercial PZQ tablets (Biltricide) in children 4 to 6 years of age infected with S. mansoni.

Children with light (1 to 99 eggs per gram of feces) or moderate/heavy (≥ 100 eggs per gram of feces) S. mansoni infection will be recruited, with a target enrollment of 40% of study participants with moderate/heavy infections and 60% with light infections, consistent with the distribution in the Phase II study.

Treatment group 1a: The efficacy and safety of a single dose of L-PZQ ODT 50 mg/kg, administered after food intake, will be assessed in 100 children 4 to 6 years of age infected with S. mansoni.

Treatment group 1b: The efficacy and safety of a single dose (40 mg/kg) of commercial PZQ tablets (Biltricide 600 mg), administered after food intake, will be assessed in this population (control arm) of 50 children 4 to 6 years of age infected with S. mansoni. A single dose of 40 mg/kg bodyweight will be used, which is the dose recommended by WHO to treat adults and school-age children and is widely used for WHO mass drug administration programs for PZQ in SSA. In a recent commentary paper by the WHO Department of Control of Neglected Tropical Diseases (Montresor and Garba, 2017)[3] and based on a recent PZQ clinical study in PSAC, the authors also recommend that in the absence of treatment alternatives, a single dose of PZQ 40 mg/kg can be endorsed for PSAC (Coulibaly et al., 2017)[4] in preventive chemotherapy programs. The efficacy results from this treatment group will serve as an internal control arm, providing a benchmark for the test regimen (Treatment group 1a).

Cohort 2

The efficacy and safety of a single dose of L-PZQ ODT 50 mg/kg, administered after food intake, will be assessed in this cohort of 30 children 2 to 3 years of age infected with S. mansoni. The number of children in this cohort is 30% of the number of children 4 to 6 years of age in Treatment group 1a (n= 100), reflecting the demographic data available from Part 1 of the Phase II study in Ivory Coast, in which, among the infected children enrolled, 27% were 2 to 3 years of age and 73% were 4 to 6 years of age. Cure rates in the Phase II study were generally similar across these age cohorts.

Children with light (1 to 99 eggs per gram of faeces) or moderate/heavy (≥ 100 eggs per gram of faeces) infection will be recruited, without stratification for intensity. The primary aim of the descriptive analysis in participants 2 to 3 years of age is to explore whether the treatment effect (% cured) is generally similar to that in older children (Cohort 1).

Cohort 3

In Cohort 3, S. mansoni-infected infants and toddlers, 3 to< 24 months of age, will be treated with the L-PZQ ODT at a dose of 50 mg/kg, administered after food intake. Enrollment will begin only after the Phase II study's Safety Monitoring Committee (SMC) has reviewed the safety/efficacy data available on 10 participants from Cohort 8 enrolled in Part 2 of that Phase II study, MS200661-0005, and found these data to be satisfactory.

The overall number of participants in Cohort 3 is 25 or more, to achieve 65 patients in pooled analysis with Cohorts 8 and 9 of the Phase II study.

The primary aim of the descriptive analysis in participants 3 to 24 months of age is to explore whether the treatment effect (% cured) is generally similar to that in older children (not an independent proof of efficacy in this subgroup). Since the number of participants in this cohort is limited in this study, the efficacy results will be pooled with those from Cohorts 8 and 9 of the Phase II study (up to 30 participants in the 13 to 24 months of age cohort and up to 10 participants in the 3 to 12 months of age cohort) to assess if treatment effect is generally similar across age groups.

Cohort 4

The efficacy and safety of a single dose of L-PZQ ODT 50 mg/kg, administered after food intake, will be assessed in 60 children 3 months to 6 years of age infected with S. haematobium. Children with light (< 50 eggs/10 mL of urine) or heavy (≥ 50 eggs/10 mL of urine) infection will be recruited. After 30 participants in Cohort 4 are treated, the efficacy and safety data will be evaluated by the IDMC to decide whether there is a need to increase the dose to 60 mg/kg. If a dose increase is needed, 30 additional participants will be added to this cohort (i.e., total sample size of 90 for Cohort 4, n= 60 total on the final dose) and treated with the 60 mg/kg dose.

The primary aim of the descriptive analysis in this cohort is to summarize safety and efficacy of the PZQ ODT in children 3 months to 6 years of age infected with S. haematobium (not as an independent proof of efficacy in this subgroup).

4.2.5 Endpoints

The primary and secondary efficacy endpoints are the same as those used in the Phase II study. A palatability outcome is added in this study.

Primary efficacy outcome: cure rate

Clinical cure is defined as no parasite eggs in the stool (S. mansoni) or urine (S. haematobium) samples at a follow-up visit.

Safety outcome

To assess the safety of a single dose of PZQ (all cohorts), the following will be collected:

- Occurrence, nature, severity and outcome of AEs,
- Occurrence of treatment-related AEs,
- Changes in laboratory safety parameters (haematology, biochemistry, urinalysis) and vital signs (body temperature, blood pressure [BP] and pulse rate).

Secondary efficacy outcome: Egg reduction rate (ERR)

The WHO guideline for morbidity control of schistosomiasis (Assessing the efficacy of antihelminthic drugs against schistosomiasis and soil-transmitted helminthiases, WHO, Geneve, Switzerland, 2013) recommends measurement of group-based ERR 2 to 3 weeks after PZQ drug administration, as an appropriate parasitological indicator for morbidity control. Thus, in this study, ERRs using group-based means will be calculated for each of the cohorts. The individual ERR will also be calculated by measuring the percent reduction of egg counts for each individual.

Secondary efficacy outcome: Cure rate by POC-CCA®

Cure rate by POC-CCA®, defined as no parasite antigens in urine as assessed by the commercially available POC-CCA® assay for S. mansoni.

Secondary outcome: Acceptability of the Study Intervention

Reaction to Study Intervention administration (e.g., spitting, crying) will be recorded, to describe tolerability as assessed by nurse/site staff for all children enrolled in the study.

The palatability assessment will use a human gustatory sensation test (100-mm VAS) scoring modified by the incorporation of a 3-point facial hedonic scale for all children 5 and 6 years of age enrolled in the study.

Secondary outcome: Pharmacokinetics

Assessment of the concentration time profile of the L PZQ ODT and Biltricide formulation in a subset of children and, if appropriate, pharmacokinetics (PK) parameters (e.g., C_{max}, t_{max}, AUC_{0-t}) of - (-)-PZQ and rac-PZQ.

4.2.6 Stratification

No stratification for male or female children will be done. It is expected that the number of children with a heavy S. mansoni infection will be low in the areas where the study will be conducted. For the moderately-infected children, we expect an overall prevalence of 32% in Ivory Coast and 24% in Kenya (Davis et al., 2015)[5]. The participants in Cohort 1 will be stratified, with target enrollment of 40% moderate/heavy infections and 60% light infection.

For Cohorts 2, 3, and 4, no stratification will be implemented. Infants and toddlers in Cohort 3 are only expected to carry light infections.

No stratification for country will be implemented. Each country is expected to contribute at least 10% to the final participant numbers to be included in the final efficacy analysis.

4.3 Justification for Dose

The dose of L-PZQ ODT (single dose of 50 mg/kg) to be used for Cohort 1 (Treatment 1a), 2, 3 and 4, has been selected based on predefined decision criteria, which combined primary and secondary efficacy and safety endpoints, from the outcome of Phase II (Part 1) study MS200661-0005, that was recently completed in African children 2 to 6 years of age infected with S. mansoni (using different doses of rac-PZQ ODTs and L-PZQ ODTs, as well as reference commercial rac-PZQ arms). In the Phase II study, the 45 mg/kg dose of L-PZQ ODT was found to be the dose with the optimal benefit/risk profile for efficacy and safety. For ease of dose calculation and implementation during public health programs (considering that the ODT tablets have a 150 mg strength), L-PZQ ODT at 50 mg/kg was selected for further development.

The single dose of 40 mg/kg bodyweight for Treatment group 1b (commercial PZQ control arm) is the recommended dose by WHO to treat adults and school-age children (http://www.who.int/schistosomiasis/strategy/en/) and is widely used for WHO mass drug administration PZQ programs in SSA. It has also been recommended by the WHO Department of Control of Neglected Tropical Diseases for use in PSAC as necessary in preventive chemotherapy programs.

The dose of L-PZQ ODT for Cohort 4 will be the same as for Treatment group 1a (50 mg/kg). Data from the meta-analysis by Zwang, et al. (2014)[1] indicated that cure rates for S. haematobium were higher or at worst 2% lower than cure rates for S. mansoni at each dose reported. Therefore, using the same dose of L-PZQ ODT for S. haematobium as for S. mansoni is appropriate. However, since L-PZQ ODT has not yet been investigated against S. haematobium, the efficacy data will be evaluated by the IDMC after 30 participants are treated in Cohort 4. In case of sub-optimal efficacy (criteria will be defined prospectively, before study start, in the IDMC charter), the IDMC could decide to increase the dose to 60 mg/kg, in which case 30 additional participants will be added to this cohort (i.e., total sample size of 90 for Cohort 4, n= 60 total on final dose) and treated with the 60 mg/kg dose.

4.4 End of Study Definition

A participant has completed the study if he/she has completed all study parts, including stool (Cohorts 1, 2, and 3) or urine (Cohort 4) sampling at the scheduled follow-up visits.

The end of the study is defined as the date of the End-of-study visit (or Extended Follow-up visit urine collection at Week 5 for Cohort 4) of the last participant.

5 Study Population

Children and infants 3 months to 6 years of age with schistosomiasis will be included in this study. As previously noted, PSAC are a high-risk group for schistosome infections and yet they are currently not treated in schistosomiasis control programs, as the current formulation is not suitable for administration to young children.

Children are viewed as vulnerable individuals, with whom risk should be kept to a minimum during the conduct of clinical research. In this study, no significant risk is anticipated to study participants at the L-PZQ ODT tested dosages of 50 mg/kg. Biltricide is approved for treatment of schistosomiasis in children ≥ 4 years of age, but it can be used to treat children below this age under medical supervision. Participants will remain in the facility for 12 to 24 hours after dosing and will be closely monitored. Laboratory safety tests are included to show that children participating in the study are not being adversely affected by the study treatment; these tests will be repeated at the end of hospitalization.

The criteria in Sections 5.1 (Inclusion Criteria) and 5.2 (Exclusion Criteria), are designed to enroll only participants who are appropriate for the study, thereby ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Participants will require the written informed consent of one of their parents or their guardian/legally authorized representative. Whenever possible, and according to local Ethical Committee requirements, a participating child's assent should be also provided. According to the EU guidance for clinical studies on pediatric populations, it is not possible to obtain assent in children 3 months to 3 years of age.

Only children meeting all inclusion criteria and no exclusion criteria may be enrolled into the study as participants. Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant, or the participant's parents or guardian/legally authorized representative has provided written informed consent, as indicated in Appendix 2.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Are

- 4 to 6 years of age (Cohorts 1 and 4)
- 2 to 3 years of age (Cohorts 2 and 4)
- 3 to < 24 months of age (Cohorts 3 and 4)

Type of Participant and Disease Characteristics

2. Are

- S. mansoni-positive (Cohorts 1, 2, and 3); diagnosis defined as positive egg counts in stool ≥ 1 egg/1 occasion) according to WHO classification [1]: light (1 to 99 eggs per gram of feces), moderate (100 to 399 eggs per gram of feces) and heavy (≥ 400 eggs per gram of feces) infections
- S. haematobium-positive (Cohort 4); diagnosis defined as positive egg counts in urine (≥ 1 egg/10 mL urine) according to WHO classification (Prevention and Control of Schistosomiasis and Soil Transmitted Helminthiasis. WHO Technical Report Series No. 912. WHO,Geneva, Switzerland, 2002).: light (< 50 eggs/10 mL of urine) and heavy (≥ 50 eggs/10 mL of urine) infections

Weight

3. Have a minimum body weight of 8.0 kg in 2 to 6 years of age children and 5.0 kg in 3 months to< 24 months of age infants and toddlers

Sex

4. Are male or female.

Informed Consent

5. Parent or guardian/legally authorized representative can give signed informed consent, as indicated in Appendix 2, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and this protocol
6. Parent's or guardian/legally authorized representative's ability to communicate well with the Investigator and his/her delegate, to understand the protocol requirements and restrictions, and to be willing to have their children comply with the requirements of the entire study, i.e.:

- To be examined by a study physician at screening, at End of Confinement Visit and 17 to 21 days after treatment
- To provide stool samples at screening (and 17 to 21 days after treatment for Cohorts 1, 2 and 3)

- To provide urine samples at screening, 12h after treatment and 17 to 21 days and 35 to 40 days after treatment
- To provide venous blood samples for laboratory assessments
- To be housed in the clinic for 12 to 24 hours
- To provide venous blood samples for pharmacokinetics (PK) assessments (for participants in the PK subset)

Additional inclusion criteria for PK sub study participants

7. Have a minimum hemoglobin level of 10 g/dl

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Findings in the clinical examination and/or laboratory safety examination on the treatment day, that in the opinion of the Investigator constitute a risk or a contraindication for the child's participation in the study or that could interfere with the study objectives, conduct or evaluation. This includes but is not restricted to bacterial or viral infections, such as dysentery, gastroenteritis, ascites, jaundice, etc
2. Participants with seizures and/or medical history of seizures and/or other signs of potential central nervous system involvement
3. Participants with known cysticercosis, or with signs or symptoms (e.g., subcutaneous nodules) suggestive of cysticercosis
4. Participants with an acute infection or other acute illness within the 7 days prior to study screening
5. Debilitating illness such as tuberculosis, malnutrition, etc

Prior/Concomitant Therapy

6. Treatment with PZQ within the 4 weeks prior to the study screening
7. Concomitant treatment (within 2 weeks prior to enrollment) with medication that might affect the metabolism of PZQ, such as certain anti epileptics (e.g., carbamazepine or phenytoin), glucocorticosteroids (e.g., dexamethasone), chloroquine, rifampicin or cimetidine (see Biltricide® Summary of Product Characteristics [SmPC])
8. Treatment within the 2 weeks prior to the study screening with anti malarial medications
9. For infants and toddlers being breast-fed, treatment of the mothers/wet nurses with PZQ in the 3 days prior to PZQ ODT administration

Prior/Concurrent Clinical Study Experience

10. Participation in any clinical study within 4 weeks prior to administration of PZQ ODT, or anticipated at any time until completion of the End-of-Study visit

Diagnostic Assessments

11. Fever, defined as temperature above 37.5°C axillary or oral
12. Mixed S. haematobium and S. mansoni infections

Other Exclusions

13. History of hypersensitivity to PZQ or any of the excipients

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Consumption of grapefruit may lead to increased PZQ levels, therefore grapefruit and grapefruit juice products will not be allowed from 24 hours before the time of Study Intervention administration until 24 hours after Study Intervention administration. During the same period, Seville orange and Seville orange juice will not be allowed.

5.3.2 Caffeine Alcohol, and Tobacco

Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until 24 hours after Study Intervention administration. Use of alcohol or tobacco is not applicable as participants are 3 months to 6 years of age.

5.3.3 Activity

Not applicable; participants in this study are 3 months to 6 years of age.

5.4 Screen Failures

This study includes both a pre screening visit between Day -28 and Day -1, and a screening visit between Day -7 and Day -1.

Participants who fail at the pre screening visit may be pre screened again; they will be assigned a new participant number at the time of the second pre screening visit.

Individuals who pass pre screening but at the time of the planned screening visit:

1. Have consumed grapefruit or grapefruit juice 24 hours prior to enrollment
2. Have been breast-fed by mothers/wet nurses treated with PZQ in the 3 days prior to enrollment
3. Have any other condition that can be normalized within the screening window

can be enrolled as soon as the temporal exclusion criterion does not apply anymore, and as long as the screening window is respected, without any need of being rescreened.

Individuals who pass pre screening but at the time of the planned screening visit:

4. Have been treated within 2 weeks prior to enrollment with anti-malarial medication or drugs that might affect the metabolism of PZQ
5. Are in need of anti-malarial medications
6. Have any other condition that can be normalized within the pre screening window of 28 days

may be rescreened at Investigator's discretion as soon as the temporal exclusion criterion does not apply anymore, and as long as the 28-day window between pre screening and enrollment is respected.

If the second screening visit is not possible to be performed within the original screening visit window (Day -7 to Day 1) then all procedures of the Screening Visit (except for the signature of another screening consent) must be repeated using the same participant screening number. Note that tests requiring additional blood may be repeated as long as the overall blood volume drawn within 4-week period does not exceed 3% of the total blood volume. Therefore, per study protocol no additional blood drawings are allowed in children below 7 kg within the 4-week period.

In this case, the same participant screening number can be kept. If the interval to the proposed Study Intervention dosing would fall outside of the 28-day window, then both pre screening and screening activities have to be repeated, and a new participant number has to be assigned.

6 Study Intervention(s)

Study Intervention is any investigational intervention (L-PZQ) or marketed product (Biltricide) intended to be administered to a study participant per the study protocol.

MSC2499550A (referred to as L-PZQ)

Chemical Name: (11bR)-2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino [2,1-a] isoquinolin-4-one

Recommended International Nonproprietary name (rINN):	R-(-)-Praziquantel
Company or Laboratory Code:	MSC2499550A
Molecular Formula:	C19H24N2O2
Relative Molecular Mass:	312.4 g/mol

White or almost white, crystalline powder.

MSC2499550A is presented as 150 mg strength.

The tablet consists of MSC2499550A combined with the following pharmaceutical grade excipients: CCI [redacted]

Praziquantel (Biltricide 600 mg)

Chemical Name: (11bRS)-2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino [2,1-a] isoquinolin-4-one

Recommended International Nonproprietary name (rINN): (RS)-Praziquantel

Molecular Formula: C19H24N2O2

Relative Molecular Mass: 312.4 g/mol

Biltricide is supplied as a white, film-coated, oblong tablet with three dividing scores.

In both countries, the German commercial product will be used. The tablet contains 600 mg of PZQ and the following inactive ingredients: CCI [redacted]

6.1 Study Intervention(s) Administration

The actual dose to be administered will be based on measured body weight. A table will be included in the Pharmacy Manual.

	Treatment group 1a: S. mansoni-infected children, 4 to 6 years of age. **Cohort 2**: S. mansoni-infected children, 2 to 3 years of age. **Cohort 3**: S. mansoni-infected children, 3 to< 24 months of age. **Cohort 4**: S. haematobium-infected children, 3 months to 6 years of age.	**Treatment group 1b**: S. mansoni-infected children, 4 to 6 years of age
Study Intervention Name:	L-PZQ ODT	Commercial PZQ (Biltricide®)
Dose Formulation:	150 mg tablet	600 mg tablet
Unit Dose Strength(s)/ Dosage Level(s):	L-PZQ ODT at 50 mg/kg For Cohort 4, the dose might be increased to 60 mg/kg after IDMC review	Biltricide at 40 mg/kg
Route of Administration:	Oral	Oral

Dosing Instructions:	Single dose of L-PZQ ODT, dispersed in water, after food intake (see Section 6.6, Dose Selection and Modification)	Single dose of commercial PZQ (Biltricide). The Biltricide tablets will be divided into 150 mg parts, crushed, suspended in water, and administered after food intake.
Supplier/ Manufacturer:	Farmanguinhos Fiocruz, Brazil	Merck KGaA (commercial product sourced from Bayer Germany)
Packaging and Labeling:	L-PZQ ODT tablets will be supplied by the sponsor in CCI [redacted]. Each CCI contains 150 tablets. Each CCI will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.	Biltricide comes in a CCI [redacted] with white closure, containing 6 tablets. CCI [redacted] Each CCI will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

The Investigator and/or designee is responsible for Study Intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the Study Intervention(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate document and returning it to the location specified. A copy will be archived for the Investigator Site File.
- Only participants enrolled in the study may receive Study Intervention(s) and only authorized site staff may supply or administer it. All Study Intervention(s) must be stored in a secure environmentally-controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions (L-PZQ ODT: CCI [redacted], and with access limited to the Investigator and authorized site staff.
- The investigator and/or designee is responsible for ensuring that the temperature at which the Study Intervention is to be stored is monitored throughout the duration of the study and that temperature records are maintained. The temperature will be recorded continuously and monitored manually twice a day.

- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- The preparation of the number of tablets for the individual subject in each cohort will be done by a pharmacist and pharmacist assistant under the responsibility of the Investigator. The pharmacy will prepare the Study Intervention for all participants per cohort according to the treatment randomization list when applicable (Treatment groups 1a and 1b) and the measured body weight in accordance with standard procedures.
- Biltricide tablets will be divided into 150 mg parts, crushed and suspended in water. L-PZQ ODT tablets will be dispersed in water. Study Interventions will be administered within one hour after food (details described in the corresponding informed consent forms) intake. Detailed procedures are described in the Pharmacy Manual.
- Study Intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused Study Intervention(s).
  - Dates, quantities, batch numbers, vial numbers, expiry dates, formulation (for Study Interventions prepared at the site), and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all Study Intervention(s) provided were fully reconciled.
- Unused Study Intervention(s) must not be discarded or used for any purpose other than the present study. No Study Intervention that is dispensed to a participant may be re dispensed to a different participant.
- A Study Monitor will periodically collect the Study Intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused Study Intervention(s) are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

The study consists of 4 cohorts, which will be enrolled in parallel. Cohort 1 includes a 2:1 randomization of children 4 to 6 years of age infected with S. mansoni to a single dose of the L-PZQ ODT 50 mg/kg (test arm; Treatment group 1a) or a single dose of the PZQ standard of care (rac-PZQ crushed tablets 40 mg/kg; Treatment group 1b). No randomization is foreseen for Cohorts 2, 3, and 4.

The participants in Cohort 1 will be stratified according to their infection intensity, with target enrollment of 40% moderate/heavy infections and 60% light infections. No stratification will be

implemented for Cohorts 2, 3, and 4. No stratification will be implemented per sex or per country.

In Treatment Groups 1a and 1b only, after confirmation of participant's eligibility and at the last practical moment prior to study intervention administration, participants will be centrally allocated to either L-PZQ ODT or Biltricide in a 2:1 ratio using a computer-generated randomization list integrated in the electronic data capturing system. Randomization will not be used to allocate participants in any of the other cohorts.

Before the study is initiated, the login information and directions for the electronic data capturing system will be provided to each site. The site will capture the participant's data in the electronic data capturing system and by completing the corresponding forms receive the study intervention group for participants of Cohort 1.

6.3.2 Blinding

Blinding Method

This is an open-label study in which participants will receive a single treatment dose of the L-PZQ ODT formulation (Treatment group 1a, Cohorts 2, 3, and 4) or the commercial PZQ formulation (Treatment group 1b) at Day 1.

Blinding of site personnel and participants/parents is not warranted in this study, since the primary efficacy assessment of egg count using the Kato-Katz method is an objective laboratory measure. Laboratory personnel will remain blinded to a participant's treatment group and screening or baseline values. To minimize bias regarding the population of participants included for analysis of the primary efficacy outcome, the list of reasons for protocol violations will be finalized before final analysis of post treatment egg counts.

6.3.3 Emergency Unblinding

Not applicable.

6.4 Study Intervention Compliance

All study interventions will be administered as dispersible tablets dispersed in water (or dispersed in water after crushing of Biltricide tablets for Treatment group 1b) under the supervision of the Investigator or designee. The study intervention administration will be recorded in the electronic case report form (eCRF).

Study intervention administration records will be used to assess compliance.

The Investigator is responsible for the control of study interventions; adequate record of receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Accountability Record, Drug Destruction Record) of the study intervention including dates, quantities and use by the study participant must be maintained.

All records and study intervention supplies must be available for inspection at every monitoring visit. When the study is terminated and study intervention accountability has been satisfactorily

completed by the pharmacist/Investigator or study drug preparer (or designee), the used and unused study drug (i.e. empty, partially used and unused containers) should be destroyed at the clinical study site after written approval by the Sponsor. The completed Drug Accountability and Drug Destruction Records will be sent to the monitor or its designee.

The site pharmacist or pharmacist assistant must maintain records of the study intervention delivery to the study site, the inventory at the site, the use by each participant and its destruction or returning after study intervention accountability has been performed by the responsible monitor. The drug-dispensing log must be kept updated, listing the identification of the participant who received drug along with the date and quantity of drug dispensed; it must be available for monitoring. Temperature of the storage location will be monitored and documented.

The Investigator will ensure that the study intervention supply is not used for any purpose other than this study.

6.5 Concomitant Therapy

All concomitant therapies (e.g., medicines or nondrug interventions) used from the time participant's parent or guardian/legally authorized representative signs the ICF until completion of the study, including any changes, will be recorded in the appropriate eCRF. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, the name, reason for use, dates administered, and dosing information will be recorded. All concomitant medications (within 7 days of participant's study treatment) received by nursing mothers of enrolled participants will be recorded on the appropriate eCRF.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.5.1 Rescue Medicine

Biltricide may be administered to address ineffective Schistosomiasis treatment. Other rescue medications may be administered to treat anticipated adverse reactions or anticipated emergency reactions.

6.5.2 Permitted Medicines

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

6.5.3 Prohibited Medicines

As referred to in the exclusion criteria (Section 5.2), administration of PZQ or use of any investigational device within 4 weeks prior to administration of the study intervention (PZQ ODT or Biltricide) and during the entire clinical study is not permitted.

If the administration of a non-permitted concomitant drug becomes necessary during the study, e.g., because of AEs, the participant should be discontinued from the study but only after consultation with the Sponsor. Children who require malaria treatment after receiving study treatment will not be withdrawn from the study, but because some anti-malarial agents (e.g.,

artemisinin derivatives) have activity against Schistosoma spp. (Liu et al, 2011)[6], they will be excluded from the primary efficacy analysis.

For children being breastfed, administration of PZQ to nursing mothers is not allowed in the 3 days prior to PZQ ODT administration (see Section 6.5).

The concomitant administration of agents that induce the drug-metabolising enzyme system in the liver (cytochrome P450), such as certain antiepileptics (e.g., carbamazepine or phenytoin), glucocorticosteroids (e.g., dexamethasone) or chloroquine, may lead to reduced plasma levels of PZQ and will not be allowed. The concomitant administration of rifampicin, which is a strong inducer of cytochrome P450, or of other cytochrome P450 inducers, is contraindicated as no therapeutically effective plasma levels of PZQ can be expected in that setting.

Similarly, the concomitant administration of agents that inhibit the cytochrome P450 system, e.g., cimetidine, may lead to increased plasma levels and a prolonged retention period of PZQ and will not be allowed.

As consumption of grapefruit may lead to increased PZQ levels, grapefruits and grapefruit juice products will not be allowed during confinement. In case a participant may have been enrolled and dosed after grapefruit consumption, a protocol deviation will be issued, however participants will not be discontinued from the study and data won't be excluded from the analysis. The Investigator will need to enquire the eventual consumption of grapefruit in the 24 hours before enrolment and ensure that the child eats only the standard meals during confinement. At discharge, he will explain the parent/guardian/legally authorized representative the importance of abstaining from grapefruit consumption until 24 hours after the study intervention administration.

Also, any medication from screening until the End-of-Study visit is not allowed without prior approval from the Investigator (except for occasional use of paracetamol or ibuprofen). All medications that are administered from screening through the End-of-Study visit will be recorded on the appropriate eCRF.

6.5.4 Other Interventions

Any unplanned diagnostic, therapeutic, or surgical procedure performed from screening through the End-of-Study visit or Extended follow-up visits (for patients in Cohort 4 with a 60 mg/kg dose) must be recorded in the concomitant procedure section in the eCRF, including the date, indication and description of the procedure(s) and outcome.

Any other special considerations, e.g., concerning food, caffeine and physical exercise, should be noted.

6.6 Dose Selection and Modification

This is an open-label study in which participants will receive a single treatment dose of the new L-PZQ ODT (Treatment group 1a, Cohorts 2, 3, and 4) or the commercial PZQ formulation (Treatment group 1b) at Day 1. Therefore, no dose modification is applicable.

If the participant vomits or spits the L-PZQ/Biltricide after dosing, he/she will not receive a new dose of L-PZQ/Biltricide. If vomiting occurs, water and/or food may be given at the Investigator's discretion and this will be documented in the CRF. Subjects will not be excluded from the analysis.

An IDMC will evaluate the interim safety and efficacy data after 30 participants are enrolled and treated in Cohort 4. The data will be summarized and evaluated to decide whether there is a need to increase the dose to 60 mg/kg in Cohort 4 (see Section 9.4.4).[5]

6.7 Treatment Intervention after the End of the Study

Participants who were positive for S. mansoni or S. haematobium but were not enrolled in the study, or enrolled patients who were not found to be cured at the End-of-Study visit, may be offered treatment with the locally available PZQ 600 mg tablets based on national recommendations.

6.8 Special Precautions

The medication administration part of the study will be conducted in a setting with access to basic emergency facilities. Equipment and other agents (epinephrine, prednisolone equivalents, etc.) will be made available at the study site in case of severe allergic reactions.

Participants will be observed when receiving the study intervention. They will remain in the facility for at least 12 hours after dosing and will be closely monitored.

6.9 Management of Adverse Events of Interest

No clinically significant risk is anticipated to participants at the tested dose. Participants will remain in the facility for at least 12 hours after dosing and will be closely observed. A participant may be confined for up to 24 hours in the event of any AE requiring prolonged observation. Based on the PK properties of PZQ, drug-related AEs (mentioned in Section 8.2) are expected to occur within approximately 12 hours after dosing. In the event that a participant stays in the clinic due to reasons other than an AE or serious adverse event (SAE), the discharge time will be in line with at least 12 hours and the additional stay will not be reported as an AE. In addition, follow-up of AEs will be performed, if required, during the first week after dosing (see Section 1.3, Schedule of Activities) but not necessarily in the facility.

[5] An Independent Data Monitoring Committee (IDMC) meeting was held on the 09 March 2020 and a decision was made to increase the dose in Cohort 4 to 60 mg/kg.

AEs will be managed in the participating health facility by study medical doctors who will remain in the facility during the study.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Not applicable.

7.2 Participant Discontinuation/Withdrawal from the Study

This is a single-dose treatment study. If a participant withdraws prior to administration of the study treatment, the End-of-Study visit will be performed and no attempts will be made to collect additional data. No further evaluations will be performed, except for safety purpose when applicable.

- A participant may withdraw from the study at any time, upon request of participant's parent or guardian/legally authorized representative (i.e., withdrawal of consent) or if the child communicates (verbally or opposing resistance) that he/she is unwilling to continue, and without giving a reason. However, the reason should be obtained when it is possible to do so, and then the reason should be reported in the appropriate Case Report Form.
- The participant may be withdrawn by the Investigator due to participation in another clinical study.
- The participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- The participant may be withdrawn if lost to follow-up.
- If a participant withdraws from the study, no further evaluations should be performed, and no attempts should be made to collect additional data, with the exception of safety data, which should still be collected if possible, but not captured in the database.
- If a participant is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.
- Data obtained prior to a participant's withdrawal will still be included in the efficacy and safety analysis.
- Participants withdrawn from the study will not be replaced.

7.3 Lost to Follow-Up

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wants to or should continue in the study. Every effort will be made to undertake a final examination visit as soon as possible and perform all procedures of the End-of-Study visit.
- Before a participant is deemed "lost to follow-up", the Investigator or designee must make every effort to regain contact with the participant. Contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

Study assessments and procedures and their timing are summarized in the Schedule of Activities (Section 1.3). Details are given in the following paragraphs.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

No protocol waivers or exemptions are allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Pre-screening

Study participants will be selected from communities living in the regions of departments of Biankouman and Man in the Tonkpi region, as well as Facobly and Kouibly in the Guémon region, Man, Ivory Coast and around the shores of Lake Victoria around Homa Bay and Mbita in Homabay County, Kenya. Prior to study onset, a list of all children 3 months to 6 years of age living in the selected areas will be prepared using records obtained from the latest census. At study beginning, the households in the villages will be informed about the study through community meetings. Prior to performing any study assessments that are not part of routine medical care, the Investigator or an appropriate designee (if local regulations permit) will obtain written pre screening consent from one of the parents or the guardian/legally authorized representative of the potential participant to allow the diagnostic activities and the identification of schistosomiasis infected children, as described in Appendix 2.

Parents or guardians/legally authorized representatives of participants will be provided with plastic containers labeled with unique identification numbers (IDs) at the first day of pre screening. Parents or guardians/legally authorized representatives of children 3 to < 24 months of age will be provided with urine collecting bags specifically designed for babies. They will be instructed to collect stool and urine samples of the child, each in one of the two separate containers. Stool and urine samples may not be processed on the same day.

Pre screening diagnosis of S. mansoni infected participants (Cohorts 1 to 3)

Pre screening diagnosis of S. mansoni infection will be done using a single POC-CCA urine cassette test. POC CCA cassettes will be classified as either positive or negative, according to the manufacturer's instructions, with further stratification depending on the strength of the color reaction. Thus, positive cassettes will be classified as + 1 (when result line is easy to see but still weak), + 2 (when result line is dark, but lighter than the control line) or + 3 (when result line is as dark as or darker than the control line). Participants who are positive in the POC-CCA test will be further screened with the aim of:

- Assessing S. haematobium co-infection using the urine filtration technique. A urine sample (about 10 mL) will be filtered through a filter mesh, and the mesh will then be examined under the microscope for S. haematobium egg count. A diagnosis of S. haematobium is defined as positive egg count of S. haematobium in urine (> 1 egg/10 mL of urine) according to WHO classification (WHO, Geneve, Switzerland, 2002) light (< 50 eggs/10 mL of urine) and heavy (≥ 50 eggs/10 mL of urine) infections. Per Section 5.2 (Exclusion Criteria), a child infected with both S. mansoni and S. haematobium cannot participate in this study.
- Assessing infection intensity at baseline using the Kato-Katz method: One stool sample will be collected during the pre screening period (Day -28 to Day -1) and the second one within a maximum of 5 days thereafter as baseline. In case the stool collection will not be possible within a maximum of 5 days between the samples, 2 other stool samples could be collected again (maximum 3 times over 28 days). Three Kato-Katz thick smears (41.7 mg) will be prepared from each of the stool samples. Infection intensity (expressed as egg count per gram of stool [epg]) will be calculated for each individual. A diagnosis of S. mansoni is defined as positive egg counts of S. mansoni in stool (> 1 egg/1 occasion) according to the WHO

classification: light (1 to 99 eggs per gram of feces), moderate (100 to 399 eggs per gram of feces) and heavy (≥ 400 eggs per gram of feces) infections.

Pre screening diagnosis of S. haematobium infected participant (Cohort 4)

The pre screening diagnosis for S. haematobium infected participants will take place in a geographical area where the prevalence of this parasite is expected to be high and the prevalence of S. mansoni low. As S. haematobium and S. mansoni co-infected children will not be included in this study (see above), children will provide:

- A stool sample from which two Kato-Katz thick smears (41.7 mg) will be prepared and observed under a microscope to assess S. mansoni infection, defined as positive egg counts of S. mansoni in stool (> 1 egg/1 occasion).
- Three urine samples to asses S. haematobium infection with the urine filtration technique. The first sample will be collected during the pre screening period (Day -28 to Day -1) and the second and the third one within a maximum of 5 days thereafter as baseline. In case the urine collection will not be possible within a maximum of 5 days among the samples, 3 other urine samples could be collected again (maximum 3 times over 28 days). Each urine samples (about 10 mL) will be filtered through a filter mesh, and the mesh will then be examined under the microscope for S. haematobium egg count (see above for infection classification). One positive sample out of three is sufficient for a positive diagnosis.

CCI [redacted]

At the pre screening visit, a Rapid Diagnostic Test (RDT) to detect malaria infection (one blood sample collected by finger puncture) can be performed at investigator's discretion. Treatment of malaria will be undertaken according to national guidelines.

At the pre screening visit, the following data will be collected: date of birth, date of pre screening consent signature, gender and race.

Screening

Children who have tested positive for S. haematobium (only) and children who have tested positive for S. mansoni (only), together with one of their parents or guardians/legally authorized representatives, will be invited to the study hospital.

Prior to performing any study assessments that are not part of routine medical care, the Investigator or an appropriate designee (if local regulations permit) will obtain written informed consent as specified in Appendix 2 to allow participation in the study and the completion of the study procedures, from one of the parents or a guardian/legally authorized representative of the participant.

Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes, provided the

procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (see Section 1.3).

During the screening period, the following tests/information-gathering will be performed within a maximum of one week prior to treatment initiation:

- Clinical safety laboratory evaluations: haematology, biochemistry and urinalysis. All biological assessments will be performed in a fasted condition, if possible, except for breast-fed babies.
- A Rapid Diagnostic Test (RDT) to detect malaria infection (one blood sample collected by finger puncture). This procedure might be performed either in the hospital or in the village, for operational purposes.
- Demographic data, consisting of date of birth, gender and height
- Medical history, including occurrence of seizures, and consisting of all previous diseases considered relevant (relevant is defined as needing medical treatment for at least 1 week) by the Investigator.
- All previous medications received within the last 6 months as considered relevant by the Investigator (relevant is defined as pre scribed to treat a relevant disease as described above)
- Complete physical examination (see Section 8.2.2) including body weight
- Vital signs in supine position (see Section 8.2.3) including:
  - BP (systolic and diastolic) – to be assessed at least 5 minutes after resting
  - Pulse rate – to be assessed at least 5 minutes after resting
  - Body temperature. This procedure might be performed either in the hospital or in the village for operational purposes.

All observed AEs and Concomitant Medications will be reported in the CRF.

Food will be provided within one hour from dosing.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.

Treatment period

Participants will be hospitalized from the morning of dosing until at least 12 hours after Study Intervention administration. During this time, participants will be monitored for AEs by study site staff.

In case several assessments are planned at the same time point, the PK samples will be taken at the pre-defined time point. Vital signs will be recorded before PK samples.

Pre dose assessments

Participants will undergo physical examination, vital signs assessment and re check of eligibility criteria. If assessments have been done on the same day they do not need to be repeated. PK samples will be taken immediately prior to dosing.

Post dose assessments

PK samples will be taken according to the sampling scheme (see Sections 1.3 and 8.5). The allowed deviation from the pre-specified assessment will be ±10% (in minutes) of the scheduled time point. In case several assessments are planned at the same time point, the PK samples will be taken at the pre-defined time point.

Vital signs will be recorded 8 hours after first dosing and again at the end of confinement (12 to 24 hours after dosing), when a physical examination will also be performed.

Clinical safety laboratory evaluations (i.e., hematology, biochemistry and urinalysis) (Section 8.2.4) will be conducted 12 hours after dosing. All biological assessments will be performed in a fasted condition if possible, except for those in breast-fed infants.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 17 mL (see Appendix 6 Pharmacokinetic Blood Sampling). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

In case the participant, due to logistical or social reasons, will have to spend an additional night in the hospital, the end of confinement will be documented and the additional night will not be considered as part of confinement. As such, it will not qualify as an SAE, as described in Appendix 3.

Follow-up visits

During the 3 days following their release from the hospital, participants will be monitored by the nurses in the health areas and/or by the community agents of the different localities for potential AEs. If an AE is observed, the nurse/community agent will need to inform the medical team in charge of the study for the necessary follow-up.

At the End-of-Study visit (between Days 17 and 21), participants from Cohorts 1, 2, and 3 will be asked to provide two stool samples (the first one will be collected within the 17 to 21 day window and the second one within a maximum of 5 days following collection of the 1st sample) and one urine sample (about 10 mL) for analysis using the Kato-Katz and POC-CCA tests respectively.

Cohort 4 participants will be asked to provide three urine samples (about 10 mL each), within 5 days, for analysis by the filtration method at the End of Study Visit between Days 17 and 21, as well as the Extended Follow-up Visit (between Day 35 and 40).

CCI [redacted]

The following tests and information gathering will be also performed:

- Vital signs in supine position (see Section 8.2.3)
- Complete physical examination (see Section 8.2.2)

If a participant withdraws prematurely from the study, every effort will be made to undertake a final examination visit as soon as possible and perform all procedures associated with the End-of-Study visit.

Any ongoing medically relevant abnormal findings at the End-of-Study visit, will be followed up until resolution or stabilization (according to Appendix 3)

8.1 Efficacy Assessments and Procedures

8.1.1 Assessment of Primary Efficacy Endpoint

The primary endpoint of this study is clinical cure rate based on objective assessment of egg counts in Cohort 1. To assess clinical cure in the 4 to 6 years of age children infected with S. mansoni (Cohort 1, Treatment Groups 1a and 1b), epg will be quantified 17 to 21 days after treatment, as determined by the Kato-Katz thick smear method described by WHO (2013). The method will be identical to the one used in the Phase II study. Two stool samples will be collected within a maximum of 5 days during the pre screening period (Day -28 to Day -1) as baseline. Two additional stool sample will be collected at the End-of-Study visit, one between 17 and 21 days after dosing, and another one within a maximum of 5 days later to determine efficacy. Three Kato-Katz thick smears will be prepared from each of the stool samples and read under the microscope. To meet the primary efficacy endpoint, a participant must have no S. mansoni eggs in any of the Kato-Katz smears collected after the dosing.

8.1.2 Assessment of Secondary Efficacy Endpoints

The epg will be determined 17 to 21 days after treatment by the Kato-Katz method as described above and ERR (in %) using group-based means will be calculated for each of the cohorts. The individual ERR will also be calculated by measuring the percent reduction of egg counts for each individual.

The assessment of clinical cure in Cohorts 2 and 3 will be done as described above using the Kato-Katz method.

Clinical cure in Cohorts 1, 2, and 3 will also be assessed using the point-of-care POC-CCA® test, following the manufacturer's instructions. One urine sample will be collected 17 to 21 days after treatment. After applying the urine, any CCA antigen that may be present in the sample binds to the labeled monoclonal antibody immobilized on the sample membrane. The solution then runs over the strip, where the antigen-antibody complex attaches to another monoclonal

antibody immobilized at the test line. A pink-colored line develops. The intensity of the line is qualitatively related to the intensity of the infection. The absence of a line indicates that no Schistosoma antigens are detected and is indicative of clinical cure.

Cure rate as assessed by the POC-CCA® assay will be evaluated for correlation with cure rate and ERR using the Kato-Katz method.

For Cohort 4, the cure rate will be determined using the urine filtration method as described in the Study Procedure Manual. To be considered cured, a participant must have no S. haematobium eggs in the urine samples collected at a follow-up.

8.1.3 Surrogate Endpoints

Not applicable

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information).

The undesirable effects after administration of PZQ depend on dosage and duration of the therapy and of kind, extent and localization of parasitic infestation, as well as duration of infection. These are mostly transient complaints, not generally requiring any special treatment. Adverse reactions may partly represent endogenous reactions to the killing of the parasites by PZQ. The following side effects of Biltricide were observed generally, in order of severity: malaise, headache, dizziness, abdominal discomfort with or without nausea, rise in temperature and urticaria. Such side effects may be more frequent and/or serious in patients with a heavy worm burden.

8.2.1 Post Marketing Adverse Event Reports for PZQ

Additional AEs reported from worldwide post-marketing experience and from publications with PZQ include: abdominal pain, allergic reaction (generalized hypersensitivity, including polyserositis), anorexia, arrhythmia (including bradycardia, ectopic rhythms, ventricular fibrillation, atrioventricular blocks), asthenia, bloody diarrhea, convulsion, eosinophilia, fatigue, myalgia, pruritus, rash, somnolence, vertigo and vomiting. For further details refer to the Biltricide® Summary of Product Characteristics (SmPC).

Table 2 Known Adverse Reactions to PZQ

Organ class	Common ≥ 1/100 to < 1/10	Very rare < 1/10,000	Not known
Cardiac disorders		Unspecific arrhythmia	
Gastrointestinal disorders	Abdominal pain Nausea Emesis		
General disorders and administration conditions	Weakness Fatigue Increased body temperature		
Hepatobiliary disorders		Hepatic coma (depending on the type of parasite in advanced disease stages)	
Metabolism and nutrition disorders	Lack of appetite		
Nervous system disorders	Headache Dizziness Lightheadedness		Convulsions (After the intake of PZQ for treating tapeworm infection, convulsions have occurred in rare individual cases; these have proven to be a reaction to co-existing neurocysticercosis. Such cases, which may occur especially in endemic regions of Taenia solium (Cysticercus cellulosae), should be clarified as quickly as possible.
Skin and subcutaneous tissue disorders	Urticaria		

The completed Phase I studies (MS200585-001 and MS200661-001) confirmed the established good safety profile for the PZQ ODTs in healthy volunteers. No SAEs were reported, and no new types of treatment related AEs were observed. The following TEAEs occurred: abdominal

discomfort, dizziness, fatigue, headache, nausea and rash (listed in the Reference Safety Information, see rac-PZQ ODT and L-PZQ ODT IBs). TEAEs were mild to moderate in severity, and generally resolved spontaneously within a few hours. The recently completed Part 1 of the Phase II study in 2 to 6 years of age children infected with S. mansoni (Study MS200661-0005) also confirmed the well-established favorable safety profile of the rac-PZQ and L-PZQ ODTs.

Newly reported PZQ-related AEs are not anticipated in this Phase III study, but they may occur. In particular, given the size of Treatment group 1a and the 2:1 randomization between Treatment groups 1a and 1b, AEs may be seen in Treatment group 1a that are not seen in other cohorts; these may be seen by chance alone and do not reflect a real difference in the safety profile in this cohort.

Participants will remain in the facility for at least 12 hours after dosing and will be closely observed. Based on the PK properties of PZQ, any drug-related adverse reactions are expected to occur within approximately 12 hours after dosing. In addition, follow-up of AEs will be performed, if required, during the first week after dosing (see Section 1.3). Laboratory safety testing is included at baseline and 12 hours after drug administration. As per the L-PZQ ODT IB and literature review, no specific safety laboratory parameter abnormalities are found after administration of PZQ; only non specific inflammatory parameters have been reported, which could be due to the underlying infection.

At each study visit, the parent or guardian/legally authorized representative (and the children, if they are able) will be queried on changes in the participant's condition. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, whether reported by the participant's parent or guardian/legally authorized representative or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period will be reported on an ongoing basis in the appropriate section of the eCRFs. All SAEs must be additionally documented and reported using the appropriate Serious Adverse Event Report Form.

Each AE report will include a description of the event, its duration (onset and resolution dates and times), its severity, its causal relationship (as assessed by the Investigator) with the study treatment, any other potential causal factors, any treatment given, or other action taken, and its outcome. In addition, serious cases will be identified, and the appropriate seriousness criteria documented.

Specific guidance will be provided in the Case Report Form Completion and Monitoring Conventions provided by the Sponsor or by the CRO.

8.2.2 Physical Examinations

Physical examination will be done according to local procedures. Refer to the Schedule of Activities (Section 1.3) for the time points.

A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Muscular, Gastrointestinal and Neurological systems.

Height and weight will be measured and recorded at screening (before dosing); weight will be measured again at the end of confinement (12 to 24 hours after dosing). Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.3 Vital Signs

Axillary temperature, pulse rate, respiratory rate, and blood pressure will be assessed according to the study schedule in the Schedule of Activities (Section 1.3).

BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

BP and pulse rate measurements should be obtained with the participant's arm unconstrained by clothing or other material. The measurements will be obtained with the appropriate cuff size, using the opposite arm from that used for blood sampling, where possible.

Axillary body temperature will be measured using a digital thermometer. Body temperature will be taken together with measurements of BP and pulse rate.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 5, at the time points listed in the Schedule of Activities (Section 1.3). All samples should be clearly identified.

Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.

The tests will be performed by the local laboratory.

Samples for the urine, haematology and biochemistry tests will be collected in a fasted condition if possible (except for breast-fed infants), and performed by the local laboratory. Detailed information is given in the Study Procedure Manual.

The Sponsor must receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study must be forwarded to the Sponsor.

The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

8.2.5 Concomitant Medications

Eventual concomitant medications will be evaluated from Screening until the End-of-Study visit, at the time points listed in the Schedule of Activities (Section 1.3).

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE are in Appendix 3.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The AE reporting period for safety surveillance begins when the participant is initially included in the study (date of signature of informed consent) and continues throughout the study's post-treatment follow-up period, until the End-of-Study visit. AEs will be captured in the database from the Screening visit up to the End-of-Study visit.

Any SAE assessed as related to study intervention must be recorded and reported, as indicated in Appendix 3, whenever it occurs, irrespective of the time elapsed since the last administration of study intervention.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Appendix 3.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, regardless of whether reported by the participant or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs must be additionally documented and reported using the appropriate Report Form as specified in Appendix 3.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

AEs are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) and are assessed for their outcome at the End-of-Study visit. All SAEs ongoing at the End-of-Study visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is given in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable country-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the study.

In accordance with ICH Good Clinical Practices (GCP), the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of participants, affect the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions," or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

All safety reporting will be described in Safety Management Plan.

8.3.5 Pregnancy

Not applicable; participants in this study are 3 months to 6 years of age.

8.4 Treatment of Overdose

For this study, any dose of L-PZQ ODT or Biltricide greater than the highest dose planned in the Pharmacy Manual for an individual participant enrolled in the study that is ingested within a 24-hour time period will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose. As no antidote or non drug therapy is available, the Investigator should use his/her clinical judgement when treating an overdose of an investigational drug.

Even if it is not associated with an AE or a SAE, any overdose is recorded in the eCRF and reported to Global Patient Safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 3, section on Reporting Serious Adverse Events and Adverse Events of Special Interest and Dose Limiting Toxicities.

8.5 Pharmacokinetics

To get information on systemic plasma concentrations after administration of the final L-PZQ ODT formulation in the targeted pediatric age groups, a subgroup of up to 20 participants 4 to 6 years of age (Treatment group 1a), up to 15 participants 2 to 3 years of age (Cohort 2), between 5 and 10 participants 3 to <24 months of age (Cohort 3) are needed to supply blood samples for determinations of systemic concentrations of R-(-)-PZQ (and if applicable its metabolites). PK sampling from up to 15 participants in Treatment Group 1b will provide information on the systemic plasma concentrations observed after Biltricide administration. For Cohort 4, 15 participants infected with S. haematobium (Cohort 4) are needed to supply blood samples for determination of systemic concentrations of R-(-)-PZQ (and if applicable its metabolites). PK sampling from an additional 15 participants will be collected for the 60 mg/kg dose group in Cohort 4. A separate written informed consent will be obtained for PK sampling. Only participants with minimum hemoglobin of 10 g/dL will be asked to take part in the PK sub-study.

Blood samples of approximately 1 mL per time point will be collected for measurement of plasma–concentrations of R-(-)-PZQ (or rac-PZQ) and, if applicable, of its metabolites, immediately prior to dosing (pre dose) and thereafter (post-dose), up to 12 hours after dosing, as specified in the Schedule of Activities (Section 1.3). Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of drug administration and each sample will be recorded in the eCRF.

As the known variability of systemic PZQ concentrations and PK parameters is high in adults, the number of participants in each PK subgroup is not based on statistical considerations but on feasibility assessments. Children weighing 5 kg to less than 7 kg will have 4 PK samples taken, children weighing 7 kg to less than 10 kg will have 7 PK samples taken, and children weighing 10 kg and above will have the full PK sampling scheme with 9 PK samples taken. For background information please see "Appendix 6 Pharmacokinetic Blood Sampling". Participants assigned to the PK sub study should fast between the dosing and 4h post dosing.

Table 3 PK sampling times per body weight group

Body weight range (kg)	Sampling times (hours)								
	Pre dose	Post dose							
5 to < 7	No	0.5	1	2	3	-	-	-	-
7 to < 10	No	0.5	1	2	3	4	6	8	-
10 and above	Yes	0.5	1	2	3	4	6	8	12

Plasma concentrations will be tabulated and summarized using descriptive statistics. PK parameters will be calculated if possible as appropriate for the respective sampling schemes. All PK parameters will be calculated using standard non compartmental methods and the actual administered dose. Calculations will be performed using the validated software tool Phoenix®/WinNonlin 6.3® (or later) by the Pharmacokinetics/Pharmacodynamics processing group of Quantitative Pharmacology, Merck Biopharma, Darmstadt, Germany, or will be outsourced under the supervision of the Sponsor.

The following PK parameters will be calculated, when appropriate:

Table 4 PK parameters

Symbol	Definition
C_{max}	Maximum observed concentration in plasma
AUC_{0-t}	Area under the plasma concentration-time curve (AUC) from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification
t_{max}	Time to reach the maximum plasma concentration
tlag	Time prior to the first measurable (non zero) concentration

PK parameters will be evaluated and listed for all participants who provide sufficient concentration time data.

8.6 Pharmacodynamics

Not applicable

8.7 Genetics

Not Applicable

8.8 Biomarkers

Not applicable

8.9 Health Economics

Not applicable

8.10 Immunogenicity Assessments

Not applicable

9 Statistical Considerations

9.1 Statistical Hypotheses

No formal hypothesis testing is planned. Point estimates of the cure rate and two- sided 95% CI will be calculated for all cohorts.

9.2 Sample Size Determination

The primary endpoint will be the cure rate computed by treatment group on the mITT population of 4 to 6 years of age children infected with S. mansoni (Cohort 1). A total of 150 participants will be randomized 2:1 into the L-PZQ ODT treatment group or the commercial rac-PZQ (Biltricide) treatment group and analyzed similarly; however, the efficacy of the two treatments will not be compared statistically. The commercial rac-PZQ treatment arm as an active control arm will be considered an internal benchmark. The sample size of n= 150 for Cohort 1 was chosen based on the precision of the estimate of the true cure rate.

For a fixed sample size, the precision of the estimate of the true cure rate is dependent on the observed cure rate. In Part 1 of the Phase II study, MS200661-0005, the observed cure rate in the mITT population for L-PZQ ODT 45 mg/kg among children 4 to 6 years of age was 83.7% (36/43 cured; 95% CI: 69.3-93.2). With 95 participants in the Phase III mITT Analysis Set receiving L-PZQ ODT in Treatment group 1a, the lower bound of a two-sided 95% CI for a single proportion using the Clopper-Pearson exact method will extend 10.0% from the observed proportion for an expected cure rate of 73.7%. Table 5 (as follows) shows a range of lower bounds of the two-sided 95% CI if the observed Phase II results were higher than the true cure rate and a lower cure rate is observed in this Phase III study.

Table 5 Precision of estimate for a range of possible cure rates observed in Phase III

Treatment Group, N enrolled	Analysis Population, n expected	Expected Cure Rate		
		Observed in Phase III (cured/total)	Lower Bound of two-sided 95% CI[a]	Precision[b]
L-PZQ ODT 50 mg/kg (1a), N= 100	mITT[c], n= 95	86.3% (82/95)	77.7%	8.6%
		80.0% (76/95)	70.5%	9.5%
		73.7% (70/95)	63.6%	10.0%
Biltricide 40 mg/kg (1b), N= 50	mITT[c], n= 47	87.2% (41/47)	74.2%	13.0%
		78.7% (37/47)	64.3%	14.4%
		70.2% (33/47)	55.1%	15.1%
L-PZQ ODT 50 mg/kg (1a), N= 100	PP[d], n= 80	86.3% (69/80)	76.7%	9.5%
		80.0% (64/80)	69.6%	10.4%
		73.8% (59/80)	62.7%	11.0%
Biltricide 40 mg/kg (1b), N= 50	PP[d], n= 40	87.5% (35/40)	73.2%	14.3%
		80.0% (32/40)	64.4%	15.6%
		72.5% (29/40)	56.1%	16.4%

[a]Using the Clopper-Pearson exact method
[b]Defined as distance from observed cure rate to lower bound of 95% Confidence Interval (CI)
[c]Assuming 5% of participants will require anti-malarial treatments (as with Phase II experience)
[d]PP= Per-protocol, allowing for 20% of participants excluded from the per-protocol analysis

Assuming 5% of participants will need anti-malarial treatments after PZQ treatment and a 20% non-evaluable rate, a total of 150 participants will be randomized in Cohort 1, according to a 2:1 ratio, to achieve 95 mITT participants and 80 PP participants exposed to the L-PZQ ODT, and 47 mITT participants and 40 PP participants exposed to commercial rac-PZQ tablets (Biltricide). The mITT population will be used to analyze the primary endpoint. See Section 9.3 for definitions of the mITT and PP populations.

In Cohort 2, a total of 30 participants 2 to 3 years of age infected with S. mansoni will be enrolled to assess consistency of the treatment effect with that in the older age group. As described in Section 4.2.4, the size of Cohort 2 is 30% of that of Treatment group 1a, to be roughly consistent with the distribution of children 2 to 3 years of age (27%) and 4 to 6 years of age (73%) enrolled in the Phase II study, in which no differences in cure rate by age were observed.

In Cohort 3, overall a total of up to 65 participants 3 to 24 months of age infected with S. mansoni will be enrolled in the Phase II and Phase III studies. The sample size in either study alone is too small to have adequate precision on the cure rate, thus the results in this Phase III study (Cohort 3) will be pooled with Cohorts 8 and 9 of the ongoing Phase II study (MS200661-0005). In the Phase II Study MS200661-0005, 20 out of 30 planned participants 13 to 24 months of age and 4 out of 10 planned participants 3 to 12 months of age were enrolled in the study. In Cohort 3 of this Phase III study, at least 25 participants 3 to 24 months of age infected with S. mansoni (i.e., ~20% of the total number of participants 2 to 6 years of age receiving L-PZQ ODT) will be enrolled. Since the enrollment of this age group from Phase II was lower than planned, more than 25 participants will be enrolled in Phase III Cohort 3 to achieve a total of 65 participants in this age group. This pooled sample will allow a general comparison to assess whether the treatment effect is similar across age groups.

A maximum of 90 children will be enrolled in Cohort 4. A total of 60 children in Cohort 4, 3 months to 6 years of age infected with S. haematobium, will be treated with L-PZQ ODT at the final dose, either 50 mg/kg or 60 mg/kg. Sample size is based on the number of participants needed to provide a meaningful estimate of cure rate in the S. haematobium-infected participants. Assuming 5% of participants will need anti-malarial treatments after PZQ treatment, the 60 enrolled participants are expected to yield at least 57 mITT participants. With at least 57 mITT participants and an expected cure rate of 75%, the two-sided 95% CI will have 13.2% precision from the observed cure rate. Assuming a non-evaluable rate of 20%, the 60 enrolled participants are expected to yield at least 48 PP participants. With at least 48 PP participants and an expected cure rate of 75%, the two-sided 95% CI will have 14.6% precision from the observed cure rate.

Calculations are based on a 2-sided 95% CI for proportions using the exact (Clopper-Pearson) method (R Software, version 3.4.2, Vienna, Austria).

9.3 Populations for Analyses

The analysis populations are specified below, in Table 6. The final decision to exclude participants from any analysis population will be made during a blinded data review meeting prior to database lock.

Table 6 Analysis populations

Population	Description
Enrolled	All participants who sign informed consent.
Intention-to-treat	The Intention-to-Treat (ITT) Analysis Set will include all participants enrolled.
Modified Intention-To- Tr eat	Modified intention-to-treat (mITT) Analysis Set includes all enrolled participants who receive one dose of treatment and who have baseline measurement. Children who require malaria treatment after enrollment in the study will not be included in the mITT Analysis Set. The primary analysis of this study will be performed on the mITT Analysis Set.
Per-Protocol	Per-protocol (PP) Analysis Set includes all participants who are in the mITT population and have one post baseline measurement without any clinically important protocol deviations. Details of the criteria for exclusion from the PP population will be provided in the Statistical Analysis Plan planned to be finalized before first participant being dosed. An additional determination will be made prior to database lock, based on a review of data (without knowledge of treatment assignment for Cohort 1) accrued during the conduct of the study.
Safety	The Safety Analysis Set will include all participants who receive a dose of study treatment. Participants will be analyzed according to the actual treatment they receive.

9.4 Statistical Analyses

All endpoints will be analyzed descriptively. Graphs will be produced as appropriate. Descriptive statistics for categorical endpoints will include frequency counts and percentages. For proportion endpoints, the calculation of 95% CIs will be based on the Clopper-Pearson (exact) method.

Descriptive statistics for continuous endpoints will include: number of available observations, mean, standard deviation, median, lower quartile, upper quartile, minimum, and maximum. For continuous endpoints, the 95% CI around the mean will be calculated where applicable.

9.4.1 Efficacy Analyses

The primary efficacy analysis will be performed on the mITT population of Cohort 1. The primary endpoint of cure rate will be calculated as the percentage of egg-positive participants at baseline who become egg-negative after treatment (as assessed by the Kato-Katz method). The exact 95% CI will be calculated based on the Clopper-Pearson method. Cohorts 2, 3, and 4 will be analyzed similarly.

The secondary endpoint of cure rate by POC-CCA® (Cohorts 1, 2, and 3) will be analyzed in the same manner as the primary endpoint, with proportion cured and its 95% CI.

The secondary endpoint of ERR will be analyzed for each of the cohorts and treatment group (Cohort 1) as group-based ERR (arithmetic and geometric) and as individual ERR (arithmetic and geometric).

Subgroup analyses will also be conducted by severity of infection (light vs. moderate/heavy infection stratification factor), country and gender. In Cohort 4, subgroup analyses will also be done by specific age groups (e.g., 3 months to 24 months of age, 2 to < 4 years of age, 4 to 6 years of age).

Sensitivity analyses may be performed on the ITT population of Cohort 1, to determine the impact of participants requiring malaria treatment, and on the PP population of Cohort 1, to assess the impact of any protocol deviations (such as completing study assessments outside the Day 17 to 21 window).

Analysis of Cohort 3 will be a pooled analysis, including the mITT population from this study and the mITT population for participants 3 to 24 months of age in the Phase II study MS200661-0005 (Cohorts 8 and 9). A logistic regression model with adjustment for study and site variability will be used to estimate cure rate.

Analysis of Cohort 4 will be performed only on the mITT population and using the same methods as for Cohort 1.

Imputation will be needed for participants in the mITT Analysis Set but not in the PP Analysis Set. For continuous endpoints, the imputation method of last observation carried forward will be used for missing data at the post baseline measurement. For binary endpoints, the imputation method of worst case will be used for missing data at the post baseline measurement. The baseline egg count for participants with missing follow-up egg count will be carried forward for both ERR and cure rate calculations, such that these participants will be considered "no change" and "not cured", respectively, for purposes of the efficacy analysis. This is equivalent to the "missing = non-responder" approach. For the 60 mg/kg dose group in Cohort 4, if egg count at Extended Follow-up is missing, egg count from End of Study visit will be carried forward for cure rate and ERR calculation in the analyses with imputation.

Sensitivity analyses will be performed to understand the impact of missing data on the primary and secondary endpoints.

Efficacy Endpoint	Statistical Analysis Methods
Primary	Cure rate as assessed by the Kato-Katz method for Cohort 1
Secondary	Cure rate as assessed by the Kato-Katz method for Cohorts 2 and 3. Cure rate as assessed by the POC-CCA method for Cohorts 1, 2, and 3. Cure rate as determined by urine filtration technique for Cohort 4. ERR from pretreatment to 17 to 21 days after treatment using Kato-Katz method for Cohorts 1, 2, and 3. ERRs from pretreatment to 17 to 21 days and 35 to 40 days after treatment using urine filtration technique for Cohort 4.
CCI	

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set, which will include all participants who receive a dose of study treatment. Participants will be analyzed according to the actual treatment they receive.

Values for all safety variables will be listed by subject and time point. Safety variables will be summarized using descriptive statistics by cohort and by treatment group (for Cohort 1).

AEs will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, and all summary tables for AEs will be organized by these categories. Frequency counts and percentages will be presented for subjects with at least 1 TEAE within each System Organ Class (SOC) and preferred term, separated by treatment group and cohort. TEAEs will also be summarized by relationship to treatment and by severity within each cohort and treatment group (for Cohort 1).

By-patient listings of clinical laboratory data and vital signs will include indications of values that are outside the reference ranges, and values that are clinically significant. Tables describing out-of-reference range shifts will be provided for clinical laboratory test results and vital signs as appropriate and by treatment arm.

9.4.3 Other Analyses

Demographic data including age, gender, height, medical history and previous medication will be provided in by-patient listings and summarized by cohort and treatment group (for Cohort 1).

PK parameters and calculations have been detailed in Section 8.5. PK analysis will also be specified in the Integrated Analysis Plan that will be finalized before database lock.

Estimation of Individual PK Parameters:

- Pharmacokinetic parameters will be calculated by the PK/PD Data Processing Group of QP, Merck, Darmstadt, Germany, or by a Contract Research Organization (CRO) selected by the Sponsor, using standard non-compartmental methods and the actual administered dose. PK parameters will be calculated using the actual elapsed time since dosing, given with a precision of 14 significant digits or the SAS format Best12. When the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data. The actual collection intervals will be used in the calculation of urine and fecal parameters.
- Non-compartmental computation of pharmacokinetic parameters will be performed using the computer program Phoenix® WinNonlin® version 6.3, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA).
- The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.1 or higher) may be used to produce tables, listings and figures and in the calculation of PK parameters if appropriate.

No other analyses are planned.

9.4.4 Sequence of Analyses

An IDMC will evaluate the interim efficacy and safety results after 30 participants are enrolled and treated in Cohort 4, in order to determine whether there is a need to increase the dose of L-PZQ ODT to 60 mg/kg in this Cohort. The IDMC will also review the safety data for all patients who have been treated with L-PZQ ODTs that are available at that time, and all efficacy and safety data of all cohorts at the end of the study.

An interim analysis for efficacy without pausing the study is planned when the first 30 subjects in Cohort 4 treated with 60 mg/kg of L-PZQ ODT have completed all assessments. The results will be available only to the internal clinical team not directly involved in the study to inform other studies in the PZQ clinical program, e.g. whether another clinical trial is necessary to evaluate the efficacy of L-PZQ ODT on S. haematobium infected children. No action to this ongoing study is planned subsequent to the interim analysis.

No hypothesis testing is planned, so no Type I error control is necessary.

10 References

[1] Zwang J and Olliaro PL. Clinical Efficacy and Tolerability of Praziquantel for Intestinal and Urinary Schistosomiasis—A Meta-analysis of Comparative and Non-comparative Clinical Trials. PLoS Negl Trop Dis. 2014;8(11):e3286.

[2] Ross AG, Vickers D, Olds GR, et al. Katayam syndrome. Lancet Infect Dis. 2007 ;7:218-24.

[3] Montresor A and Garba A. Treatment of preschool children for schistosomiasis. Lancet Glob Health. 2017; 5:640-41.

[4] Coulibaly JT, Panic G, Silué KD, et al. Efficacy and safety of praziquantel in preschool-aged and school-aged children infected with Schistosoma mansoni: a randomised controlled, parallel-group, dose-ranging, Phase II trial. Lancet Glob Health .2017;5:e688-e98.

[5] Davis SM, Wiegand R., Mulama F, et al. Morbidity associated with schistosomiasis before and after treatment in young children in [8]Rusinga Island, western Kenya. Am J Trop Med Hyg. 2015: 92 (5): 952–8.

[6] Liu R, Dong HF, Guo Y, et al. Efficacy of praziquantel and artemisinin derivatives for the treatment and prevention of human schistosomiasis: a systematic review and meta-analysis. Parasit Vectors. 2011;4:201.

11 Appendices

12 Appendix 1 Abbreviations

AE	Adverse Event
BA	Bioavailability
BP	Blood pressure
CCA	Circulating Cathodic Antigen
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CRO	Contract Research Organization
D-PZQ	Dextrorotatory enantiomer of praziquantel
DT	Dispersible tablet
eCRF	Electronic Case Report Form
epg	Egg count per gram (of stool)
ERR	Egg Reduction Rate
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-Treat
KEMRI	Kenya Medical Research Institute
L-PZQ	Levorotatory enantiomer of praziquantel
mITT	Modified Intention-to-Treat
ODT	Orodispersible Tablet
PK	Pharmacokinetics
POC-CCA	Point-of-Care Circulating Cathodic Antigen
PP	Per Protocol

PSAC	Pre school age children
PZQ	Praziquantel
Rac-PZQ	Racemic praziquantel
SAE	Serious Adverse Event
SSA	Sub-Saharan Africa
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAEs	Treatment-Emergent Adverse Events
VAS	Visual Analogue Scale
WHO	World Health Organization

Appendix 2 Study Governance

Financial Disclosure

A financial disclosure form will be signed by all investigators prior to study start and one year after completion of the study.

Informed Consent Process

Pre screening consent

Prior to performing any study assessments that are not part of routine medical care for the participant, the Investigator or an appropriate designee (if local regulations permit) will obtain written pre screening consent from one of the parents or a guardian/legally authorized representative of the participant to allow the diagnostic activities and the identification of infected children, as described in Section 8. Participants will be informed that their participation in the pre screening activities is voluntary.

Informed consent

Schistosome-positive participants after pre screening assessment, together with one of their parents or guardian/legally authorized representatives, will be invited to the study hospital, for the completion of the study procedures.

An unconditional prerequisite for each participant prior to participation in the study is written informed consent, which must be given before any study-related activities are carried out. Written informed consent will be provided by either one of the participant's parents or one of his/her guardian/legally authorized representative. If permitted by national regulations, a person other than the Investigator (designee) may inform the participant's parent or guardian/legally authorized representative about the study and sign the Informed Consent Form, as above.

A participant information sheet will be prepared in the local languages, French, Kiswahili and Dholuo, in accordance with ICH GCP, and will be provided by the Sponsor for the purpose of obtaining pre screening consent and informed consent/assent.

- The Investigator or his/her representative will explain the nature of the study to the participant and his/her parent/guardian/ legally authorized representative and answer all questions on the study, using language chosen so that the information can be fully and readily understood by laypersons.
- The participant's parent(s) or guardian/legally authorized representative will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.
- Participants must be informed that their participation is voluntary
- After the information is provided by the Investigator or an appropriate designee, one or both (according to country specific ethic requirements) of the participants' parents or his/her guardian/legally-authorized representative will be required to sign and date a statement of informed consent that meets the requirements of local regulations; ICH guidelines and the IRB/IEC.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the participant's parent(s) or his/her guardian/legally authorized representative is (are) illiterate, an impartial witness must be present during the information session. The witness will explain to the parent or guardian/legally authorized representative the information contained in the written document and ask to give verbal consent to have his/her child participating in the study. Consent of the participant's parent or guardian/legally authorized representative will be confirmed by his/her fingerprint on the form; the witness will sign and date the form.
- For children undergoing PK analysis, information concerning the necessity of further blood drawing will be provided by the investigator and an additional ICF will be signed.
- The original signed and dated declaration of informed consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.
- A copy of the signed and dated information and ICF(s) should be provided to one of the participant's parents or his/her guardian/legally authorized representatives prior to participation.
- If the ICF is updated during their participation in the study, participants must be re consented to the most current, approved version.

In case a participant is not eligible at the pre screening activities ("pre screening failure") and is pre screened again later, Section 5.4 describes the procedures to be repeated.

In case a Schistosoma-positive child is not eligible at the screening activities ("screening failure"), he/she can be re assessed, at investigator discretion. If the reassessment is performed later than 7 days after the initial screening visit, a new ICF should be obtained. If the interval from the initial pre screening consent to the proposed Study intervention dosing is greater than 28 days, then both ICFs need to be obtained again: both pre screening and screening activities have to be repeated, and a new participant number has to be assigned.

Data Protection

The obtained data will be handled strictly confidentially. For each participant, original medical data will be accessible for the purposes of source data verification by the Monitor, audits and regulatory inspections, but patient confidentiality will be strictly maintained. Personal data will be anonymized for data analysis. No names will be published at any time and published reports will not allow for identification of single participants. Anonymized blood samples will be sent to PPD for PK analysis.

CCI . Confidentiality and anonymity will be ensured throughout the entire research project.

- The Investigator will assign a unique identifier to participants after obtaining their informed consent. This number will serve as the participant's identifier in the study as well as in the clinical study database. All participant records or datasets transferred to the Sponsor will

contain the identifier only; participant names or any identifiable information will not be transferred.

Only the Investigator or designee will be able to link study data to an individual participant via an identification list kept at the site.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data.

- The Sponsor must inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the participant's parent or his/her guardian/legally authorized representative, who will be requested to give consent on data handling procedures in accordance with national regulations.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

The study will be conducted in 2 centers:

- the hospital of Man, Ivory Coast
- the Homa Bay Hospital, Kenya.

The Principal Investigators listed on the title page, PPD represent all Investigators for decisions and discussions on this study, per ICH GCP. The Principal Investigators will provide expert medical input and advice on the study design and execution and is responsible for the review and sign-off of the clinical study report.

The study will appear in the following clinical studies registries: clinicaltrials.gov and Pan African Clinical Trials Registry (PACTR).

This clinical study will be sponsored by:

Merck KGaA

Frankfurter Strasse 250

64293 Darmstadt, Germany.

The Sponsor will enlist the support of the following CRO:

PPD

Data Management service will be provided by

Triclinium Clinical Development (Pty) Ltd

Details of structures and associated procedures will be defined in a separate Manual of Operations, which will be prepared under the supervision of the Clinical Trial Leader.

The study interventions administered in this study (L-PZQ ODT and the commercial reference product, Biltricide) will be supplied and distributed by the Sponsor or designee.

An IDMC will be charged with reviewing efficacy and safety data of the first 30 participants of Cohort 4 and the available safety data for all patients who have been treated with L-PZQ ODTs up to that time. In addition, it will review safety and efficacy data for all cohorts at the end of the study. The IDMC will be chaired by a person with experience in clinical studys and with participation in IDMCs. IDMC membership will comprise at least a clinician with expertise in schistosomiasis, a pediatrician and a biostatistician.

Further details on the IDMC composition, processes and decision criteria will be provided in the IDMC charter that will be available before the start of enrollment.

The Sponsor's Global Patient Safety department, or its designated representatives, will supervise drug safety and the timeline for reporting of AEs and SAEs to all concerned parties in accordance with the applicable guidelines, laws, and regulations.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
  - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
  - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Incidental findings

- The procedure to be followed in case of any incidental findings will be described in the project management plan.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.
- When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

One of the parents or guardian/legally authorized representatives of the children participating in the study will be compensated. The compensation will include reimbursement of transport to/from the hospital, food during the hospital visits and a monetary compensation for the income loss due to the visits to the hospital. Prior to their implementation, the details of the proposed compensation will be reviewed by the applicable IEC/IRB.

Clinical Study Report

After study completion, the Sponsor or delegate will write a clinical study report in consultation with the Coordinating Investigators following the guidance in ICH Topic E3.

Publication

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter

studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by agreement.

Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

The first publication will include the results of the analysis of the primary endpoint. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication but maintains the right to delay publication in order to protect intellectual property rights.

Dissemination of Clinical Study Data

The study results will be disseminated according to Merck's policy and SOPs. The procedures for publication planning will also follow the most recent recommendations from the International Committee of Medical Journal Editors.

The specific study information and data will also be disclosed by the Sponsor publicly by registering clinical studies on publicly accessible web platforms such as www.clinicaltrials.gov prior to, during and after the completion of the clinical study in manners consistent with applicable laws and rules governing protection of patient privacy and intellectual property. In addition, the study results will be made publicly available by means of a Clinical Study Report synopsis in accordance with privacy legislation and rules. Other researchers can, by following the appropriate Merck KGaA processes, gain access to the data for additional analysis or information as part of EFPIA/PhRMA commitment to Responsible Data Sharing. Merck KGaA observes stringent data protection rules and as such has implemented a strict process whereby external researchers may apply for access to the data. All details concerning obtaining access to the clinical study data are available on a dedicated web page on the Merck KGaA website: http://biopharma.merckgroup.com/en/research_development/clinical_trials/commitment_to_responsible_clinical_trial_data_sharing/commitment_to_responsible_clinical_trial_data_sharing.html.

Data Quality Assurance

- All participant study data will be recorded on electronic CRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Study Procedure Manual.
- The Investigator must maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur

once quality control and quality assurance procedures have been completed. PDF files of the CRFs will be provided to the Investigators at study completion.

- Study monitors will perform ongoing on-site and off-site source data verification at regular intervals according to the monitoring plan, to confirm that data in the eCRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Upon initiation of the study, the Investigator or designee will be provided with an Investigator Site File containing all necessary study documents, which will be completed throughout the study and updated as necessary.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.
- The clinical study protocol, each step of the data capture procedure and the handling of the data, including the final clinical study report, will be subject to Quality Assurance activities. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all study documents and other materials at the site, including the Investigator Site File, the completed CRFs, all Study Intervention and Study Intervention accountability records, and the original medical records or files for each participant.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the following demographic and medical information for the participant, and should be as complete as possible:
  - Participant's full name, date of birth, sex, height, and weight
  - Medical history and concomitant diseases
  - Prior and concomitant therapies (including changes during the study)
  - Study identifier (Screening number) and participant's study number (enrollment number or Randomization number).
  - Dates of entry into the study (signature date on the pre screening consent and the informed consent) and each visit to the site
  - Any medical examinations and clinical findings predefined in the protocol

  - All AEs
  - Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.
- All source data must be filed (CT or MRI scan images, ECG recordings, and laboratory results and any other concomitant procedure results collected during the course of the study and for the follow-up of AEs). Each document must have the participant number and the procedure date, ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- Data recorded on printed or electronic CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The study monitors will use printouts of electronic files for source data verification. These printouts must be signed and dated by the Investigator or designee and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in ICH GCP Guideline E6 Chapter 1.51.

Study and Site Closure

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of participants by the Investigator
  - Discontinuation of further development of the Sponsor's compound

Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators must assess the severity of AEs per the Qualitative Toxicity Scale, as follows:

Mild: The participant is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the participant is unable to carry out his or her usual activities.

Expected side effects for the different research products are detailed in the investigator's brochure and in the informed consent.

Investigators must also systematically assess the causal relationship of AEs to study intervention (including any other non study interventions, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study intervention include, but may not be limited to, temporal relationship between the AE and the study intervention, known side effects of study intervention, medical history, concomitant medication, course of the underlying disease, and study procedures.

Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study intervention discontinuation or are considered otherwise medically

important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia or increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as specified below for reporting SAEs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit, that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are not to be considered AEs. However, if adverse signs or symptoms occur in association with disease progression then these should be recorded as AEs.

Pre-defined Adverse Events of Special Interest for Safety Monitoring

Healthy participants might experience diarrhea, nausea, vomiting, headache, dizziness, inflammation and abdominal pain. These symptoms are almost always transient and occur early during therapy initiation and spontaneously resolve in most cases. If any of these AEs are observed, their severity should be defined based on clinical judgment of the Investigator and defined according to the Qualitative Toxicity Scale as described above.

Recording and Follow-Up of AE and/or SAE

From screening visit to End of Study, the participant and the parents or guardian/legally authorized representative will be queried on changes in his or her condition. During the reporting period, any unfavourable changes in the participant's condition will be recorded as AEs, whether reported by the participant or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the CRF. All SAEs must be additionally documented and reported using the appropriate Serious Adverse Event Report Form as described in the following section.

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented.

Specific guidance is in the CRF completion guideline provided by the CRO.

Adverse Event Reporting Period

The AE reporting period for safety surveillance begins at screening visit, (date of signature of informed consent) and continues through the study's post treatment follow-up period until the End-of-Study visit.

Any SAE assessed as related to a Study Intervention must be reported whenever it occurs, irrespective of the time elapsed since the last administration of the Study Intervention.

Reporting Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a written report must be sent immediately thereafter by fax or e-mail. Names, addresses, and telephone and fax numbers for SAE reporting will be included in the study specific SAE Report Form.

Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the CRF.

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for

initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Monitor, although in exceptional circumstances the drug safety department may contact the Investigator directly to obtain further information or to discuss the event.

Safety Reporting to Health Authorities, Independent Ethics Committees/Indipendent Review Boards and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the IEC/IRB that approved the study.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of participants or impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File. All details about the country specific reporting requirements for Individual Case Safety Reports (ICSRs) and periodic safety reports to Health Authorities are described in the latest version of the Drug Safety Manual.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

Appendix 4 Volume of biological fluid collected during the study

Pre Screening (Day -28 to Day -1)

	Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume/weight per Sampling (approx.)	Total Volume (approx..)
C1 - C3	Stool	Parasitology	Kato-Katz	2	2 g	4 g
	Urine*	Parasitology	POC-CCA	1	100 µL	10 mL
			Filtration		10 mL	
	Blood	Parasitology	Malaria RDT**	1	20-50 µL	20-50 µL
C4	Stool	Parasitology	Kato-Katz	1	2 g	2 g
	Urine*	Parasitology	Filtration	3	10 mL	30 mL
	Blood	Parasitology	Malaria RDT**	1	20-50 µL	20-50 µL

Screening (Day -7 to Day 1)

	Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume per Sampling (approx.)	Total Volume (approx.)
C1- C4	Urine*	Urinalysis	NA	1	5-10 mL	5-10 mL
	Blood	Parasitology	Malaria RDT	1	20-50 µL	20-50 µL
		Haematology Biochemistry	NA	1	4 mL	4 mL

Treatment (Day 1) for PK sub-study participants only

	Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume per Sampling (approx.)	Total Volume (approx.,)
C1b, C4	Blood	PK	NA	4 - 9 (see Section 8.5)	1 mL	4 - 9 mL

12 hours after dosing (Day 1/Day 2)

	Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume per Sampling (approx.)	Total Volume
C1- C4	Urine	Urinalysis	NA	1	5-10 mL	5-10 mL (approx..)
	Blood	Haematology Biochemistry	NA NA	1	4 mL	4 mL

End-of-Study Visit (Day 17 to 21)

	Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume per Sampling (approx.)	Total Volume (approx..)
C1- C3	Stool	Parasitology	Kato-Katz	2	2 g	4 g
	Urine*	Parasitology	POC-CCA	1	100 µL 10 mL	10 mL
C4	Urine*	Parasitology	Filtration	3	10 mL	30 mL

Extended Follow-up Visit (Day 35 to 40)

	Body Fluid	Type of Test	Specific Test	Number of Sampling	Volume per Sampling (approx.)	Total Volume (approx..)
C4, 60 mg/kg dose group	Urine*	Parasitology	Filtration	3	10 mL	30 mL

* The same sample might be used for additional exploratory urine analyses.
**At investigator's discretion

Appendix 5 Clinical Laboratory Tests

Table 7 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet Count	RBC Indices: • MCV • MCH • MCR	WBC Count with Differential: • Neutrophils • Lymphocytes • Leucocytes
	RBC Count		
	Hemoglobin		
	Hematocrit		
Clinical Chemistry	Creatinine	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total Protein
	BUN		Bilirubin
	Glucose	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	CRP
Routine Urinalysis	• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick and gravity		
Other Screening Tests	• Malaria rapid diagnosis test performed on a blood from fingerprick • Kato Katz method on stool • POC-CCA test performed on urine • Filtration method perform on urine All study-required laboratory assessments will be performed by the local laboratory.		

Appendix 6 Pharmacokinetic Blood Sampling

The European Commission Expert Group (Ethical Considerations for clinical studys on medicinal products conducted with minors, Revision Sep 2017), in its recommendation for blood sampling in paediatrics, states that the total blood volume in paediatrics is estimated at 80 mL per kg of bodyweight. Blood loss should not exceed 3% of the total blood volume over 4 weeks, and should not exceed 1% at any single time. With this recommendation in mind, the following table was created, to summarize and ensure that the amount of blood taken from the children enrolled in this study is not excessive, and is within the recommended range.

Body Weight Range (kg)	Approx. Age	Total blood volume @ 80 ml/kg	3 % Volume (mL)	1 % Volume (mL)
6 ± 1.5 kg	3 months	480	14.4	4.8
9 ± 1.5 kg	10 months	720	21.6	7.2
12 ± 1.5 kg	2 yrs	960	28.8	9.6
15 ± 1.5 kg	4 yrs	1200	36	12
18 ± 1.5 kg	5 yrs	1440	43.2	14.4
21 ± 1.5 kg	6 yrs	1680	50.4	16.8
24 ± 1.5 kg	8 yrs	1920	57.6	19.2

The Kenyan health authority KEMRI issued a guidance 2008, stating that the volume drawn for research purposes in addition to volume needed for routine care, should not exceed 1 mL/kg, and the maximum cumulative draw volume allowed is 5 mL/kg within 8 weeks. Source: http://www.who.int/bulletin/volumes/89/1/BLT-10-080010-table-T2.html

The present study includes the following sampling:

Body Weight Range (kg)	Minimum Total blood volume @ 80 ml/kg	3 % Volume (mL)	Volume Routine Care (mL)	Volume PK (mL)	Volume Total (mL)
Not exceed 7	400	14.4	8	4	12
7 to < 10	560	16.8	8	7	15
10 and above	640	19.2	8	9	17

PK sampling was designed so as not to exceed the allowable amount of blood that can be drawn, both according to EU and KEMRI guidance.

Appendix 7 Sponsor Signature Page

Study Title:	An open label, Phase III efficacy and safety study of L praziquantel orodispersible tablets (L PZQ ODT) in Schistosoma infected children 3 months to 6 years of age, including a 2:1 randomized, controlled cohort of Schistosoma mansoni infected children 4 to 6 years of age treated with L PZQ ODT or commercial PZQ (Biltricide®)
Study Number:	MS200661-0003
Clinical Study Protocol Version / Date:	1.2 / 11 August 2020

I approve the design of the clinical study:

PPD

Signature

14.08.2020

Date of Signature

Name, academic degree:	PPD
Function/Title:	Medical Responsible
Institution:	Merck KGaA
Address:	Frankfurter Strasse 250, 64293 Darmstadt, Germany
Telephone number:	PPD
E-mail address:	PPD

Appendix 8 Coordinating Principal Investigator Signature Page

Study Title:	An open label, Phase III efficacy and safety study of L praziquantel orodispersible tablets (L PZQ ODT) in Schistosoma infected children 3 months to 6 years of age, including a 2:1 randomized, controlled cohort of Schistosoma mansoni infected children 4 to 6 years of age treated with L PZQ ODT or commercial PZQ (Biltricide®)
Study Number:	MS200661-0003
Clinical Study Protocol Version / Date:	1.2 / 11 August 2020
Site Number:	100

I am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

DocuSigned by:
PPD
PPD
PPD
PPD
17-août-2020 | 04:05:08 PDT
PPD

17-août-2020 | 04:05:17 PDT

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	Principal Investigator PPD
Institution:	PPD
Address:	
Telephone number:	
Fax number:	NA
E-mail address:	PPD

Appendix 8 Local Principal Investigator Signature Page Ivory Coast

Study Title:	An open label, Phase III efficacy and safety study of L praziquantel orodispersible tablets (L PZQ ODT) in Schistosoma infected children 3 months to 6 years of age, including a 2:1 randomized, controlled cohort of Schistosoma mansoni infected children 4 to 6 years of age treated with L PZQ ODT or commercial PZQ (Biltricide®)
Study Number:	MS200661-0003
Clinical Study Protocol Version / Date:	1.2 / 11 August 2020
Site Number:	100

I am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

DocuSigned by:
PPD
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14-août-2020 | 06:56:31 PDT

14-août-2020 | 06:56:56 PDT

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	PPD Principal Investigator
Institution:	PPD
Address:	
Telephone number: Fax number:	NA
E-mail address:	PPD

Appendix 9 Principal Investigator Signature Page Kenya

Study Title:	An open label, Phase III efficacy and safety study of L praziquantel orodispersible tablets (L PZQ ODT) in Schistosoma infected children 3 months to 6 years of age, including a 2:1 randomized, controlled cohort of Schistosoma mansoni infected children 4 to 6 years of age treated with L PZQ ODT or commercial PZQ (Biltricide®)
Study Number:	MS200661-0003
Clinical Study Protocol Version / Date:	1.2 / 11 August 2020
Site Number:	200

I am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I have reviewed this document
Signing Time: 13-Aug-2020 | 07:03:56 EDT
PPD

Signature

13-Aug-2020 | 07:04:16 EDT

Date of Signature

Name, academic degree: Function/Title: PPD Principal Investigator PPD

Institution: PPD

Address:

Telephone number: E-mail address: